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ON MEDICAL EDUCATION

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A NUMBER of years ago I attended a vaudeville show and was amused at an argument between two comedians. One said, "Go ahead, tell all you know. It won't take long." The other replied, "I'll tell all we both know. It won't take any longer."

What I have to say on medical education will not take long, nor can I claim a scientific basis for the convictions that I have acquired from some years of experience in teaching physiology and surgery in three medical schools.

Some years ago, Mr. Robert Hutchins, then Chancellor of The University of Chicago, announced that the Faculty is the chief obstacle in the way of a student's getting an education.

In his book, *The Horse and Buggy Doctor,* Arthur E. Hertzler wrote as follows about medical teaching and teachers. "I give place to no man in the appreciation of the medical researcher, but his problems are not for the medical student. Researchers should be quarantined both for their own good and for the good of the student. I speak sympathetically because I have dabbled in the borderlines myself, but I have never mentioned them to my students. The fact should be recognized that the average doctor never does catch up with what the researcher is doing. We doctors should be spared the agony of the scientific delivery room and should be allowed to hold the baby only after the nurse has him all polished up and dressed."

These are picturesque statements of the opposite of what I believe. Dr. Hertzler's position, possibly held by others, seems to be that the student learns best by the didactic method and should be spared the agony of thinking for himself. It is education by dictation. It assumes, furthermore, that the scientific babies finally do become dressed and polished and that the clothes will not later need to be changed.

Mr. Dooley was a bartender on Archer Avenue in Chicago during the early years of the century and was wont to discuss many things with his friend, Mr. Hennessy, which were recorded for a larger audience by Finley Peter Dunne.

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On the subject of education Mr. Dooley had this to say: "Children shouldn't be sent to school to larn, but to larn how to larn. I don't care what ye larn them so long as 'tis mightly unpleasant to them. 'Tis trainin' they need, Hennessy." I prefer the philosophy of the sage of Archer Avenue to that of the famous educator or the horse and buggy doctor of Halsted, Kansas. I believe that only the man who knows by experience the method of original investigation, its difficulties and disappointments, and the tentative nature of its conclusions is qualified to teach science, at least at the university level. Only the investigator can really appreciate the basis in fact for the opinion that passes as knowledge.

For a number of years I have made a practice of asking men who have been unusually successful in science or medicine what factors in their estimation were chiefly responsible for this success.

Frank Billings, Professor of Medicine in Rush Medical College, and in his day the most eminent internist in Chicago and possibly in the United States, answered my inquiry in his customary impressive way. "All that I am or have ever achieved in life I owe to Christian Fenger."

Dr. Ludvig Hektoen, Professor of Pathology in Rush Medical College, Chairman of the National Research Council, and one of our country's leading pathologists, acknowledged the contribution of his teacher in a somewhat different vein. "The fundamental function of medicine is research. Research is the base of all its activities. The treatment of disease and injury, the education and training of physicians, the education of the public, all are based on the knowledge created by research as compounded of experience, observation and experiment. Fenger's great service was that he illustrated and exemplified more than anyone else of his day in this center the mightly significance of research in medicine. In his writings the word research was used seldom, but the spirit of research prevailed in all his work as pathologist, teacher, surgeon, and consultant."

In April, 1932, the Society for Clinical Surgery held its annual spring meeting at the Mayo Clinic in Rochester, Minnesota. After the scientific sessions were over, Dr. Will Mayo invited the Society for a pleasure cruise on his yacht on the Upper Mississippi. Some thirty-five visiting surgeons, together with Drs. Will and Charles Mayo, made up the party. In the afternoon while most of the guests were outside on the deck enjoying the scenery provided by the bluffs of the Upper Mississippi, Drs. Will and Charles, having passed this way many times before, were sitting by themselves in the stateroom. Dr. Will beckoned to me to come over and sit with them. "You are not interested in our beautiful Minnesota scenery?" he inquired. "Yes," I replied. "But I am more interested in this opportunity to converse with you. Would you be willing to tell me who the medical teachers were who had the greatest influence in shaping your careers as surgeons and medical administrators?" As was his habitual custom, Dr. Charles looked up to his older brother Will as if to pass the question on to him. Dr. Will looked out of the window for some little time and then spoke with deep conviction. "We owe a lot to Drs. Mikulicz of Prague

and Joseph Price of Philadelphia. However, the man who taught us most and who was chiefly responsible for our development in medicine was one of your fellow townsmen.'' I looked at Dr. Will Mayo for a moment and then said, ''Could it be Dr. Christian Fenger?'' ''Yes,'' he said. ''Christian Fenger was the greatest teacher we ever had and the greatest influence in the development of our method of practice.''

I cite these examples because I have become persuaded that an inspiring teacher is by far the most important factor in the educational experience. The student should be brought into contact with such a man at the earliest possible time in his medical training. I deplore the recent practice in my own university of sequestering our greatest figures in science in research institutes where they come in contact only with graduate students. Such men have already been motivated and can carry on with coaching provided by a young Ph.D. with only a few years more experience.

What should the subject matter be? Here we encounter the controversial problem of the medical curriculum. I will have some comments on this later on, but for the moment, I should like to reflect on the amazing success of William Rainey Harper, the first President of The University of Chicago. While he was a great administrator, Dr. Harper apparently had a tremendous influence as a teacher, and of all subjects the one he taught was Hebrew.

I believe that the individual instructor should be given wide latitude in the methods he employs. Among my own teachers, A. J. Carlson and H. Gideon Wells taught best by the Socratic method. Their sharp questions stimulated many students to think for themselves. This was also the method of John B. Murphy. On the other hand, James B. Herrick, Bertram Sippy, Arthur Dean Bevan, and Frank Billings taught best by lectures and demonstrations. The priceless ingredient is enthusiasm for the subject and a sincere interest in the student. Only the investigator is apt to have this enthusiasm and the ability to communicate enthusiasm.

I believe Whitehead had something like this in mind in his book *The Aims of Education,* when he insisted that information must be imparted with imagination. ''For successful education there must always be a certain freshness in the knowledge dealt with. It must either be new in itself or it must be invested with some novelty of application to the new world of new times. Knowledge does not keep any better than fish. You may be dealing with knowledge of the old species, with some old truth; but somehow or other it must come to the students, as it were, just drawn out of the sea and with the freshness of its immediate importance. . . . It is in respect to the provision and utilization of these conditions for an efficient faculty that the two functions of education and research meet together in a university. Do you want your teachers to be imaginative? Then encourage to research.''

I should like to paraphrase a statement from William Osler. He who practices medicine or does research but does not read the literature sails an uncharted sea. He who reads books but does not see patients or do research never puts to sea at all.

From these previous remarks it might well be concluded that I am not greatly interested in changing the medical curriculum. This is not altogether so. I appreciate that improvements can be made. However, in making changes I believe that it is important that great care be observed not to stifle the research activities of the staff. It is also important not to destroy the morale of the teacher or to lessen his respect for his subject. The vast increase in medical knowledge of the past 30 years is uneven with respect to the areas represented by the usual departments in the medical school. In adjusting the student's time allotted to these various subjects it should be recognized that gross anatomy, for example, has become relatively less important than it once was. Perhaps this is one reason for the present scarcity of able and enthusiastic teachers in this area. In our school we have attempted to meet this problem by making use of our younger surgeons as instructors in the dissecting room. Internists have perhaps rightly claimed that further knowledge of chemistry or physiology is of more value to them than the anatomy of the extremities.

The present custom of teaching all the preclinical subjects during the first two years of the medical course should probably be re-examined. There is no one perfect place to break in on the study of medicine. Each subject is better understood if the student already knows the others. This is the reason for prerequisites. Some thought could be given to the complexity of the subject, and those that are easier to understand placed earlier in the course. Such changes might result in some clinical courses being taught to freshmen and some basic science courses to seniors. A by-product of such a development might be an increased interest in the medical course on the part of the first-year student because of contact with disease and patients and, on the part of the seniors, a better realization of the great contributions of the basic sciences in clinical problems.

When the clinical departments were established at The University of Chicago, lectures and large amphitheater clinics were abolished in favor of bedside teaching to small groups of students. This method still prevails, but we have partly returned to didactic lectures and clinics for those who teach best in this way.

Participation in research is encouraged but only about a third of the students become seriously interested. It has proved more practical to stress this method of education during the residency period. A thesis is not required for graduation.

We have made a few tentative experiments in the presentation of subjects by a group of teachers interested in a given area and drawn from both the basic science and the clinical field. While there may be certain advantages to the student in this method, it is time consuming for the teacher and there is danger that it may detract from his research activity. I should be reluctant to give up the challenge and opportunity that is presented to a young instructor when he is assigned a course to develop and teach in his own way. His success or lack of it becomes evident in the reaction of his students. If he can communicate to them a genuine love of scholarship and in the words of Mr. Dooley "learn them how to learn" the rest will follow.

EXFOLIATIVE CYTOLOGY APPLIED TO THE DETECTION AND TREATMENT OF HEAD AND NECK CANCER

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EXFOLIATIVE cytology is most commonly utilized for the detection of cancers which may be located in comparatively inaccessible anatomic sites. Since most oral pharyngeal lesions are readily accessible, it is usually preferable to take a specimen for biopsy at once. However, some lesions of carcinoma are so innocent in appearance that both the examiner and the patient may hesitate about taking a specimen and exfoliative cytology would seem to be a desirable diagnostic adjunct in such cases.

The cellular criteria of malignancy and the reliability of exfoliative cytology are fairly well established. From the clinicians' point of view the same limitations which apply to biopsy specimens also apply to exfoliative cytology; that is, negative findings are never conclusive but a positive finding can be accepted with some confidence. Since experience with oral and pharyngeal lesions of carcinoma is limited, there is some question whether or not exfoliative cytology can provide reliable specimens as frequently as biopsies.

There is an extensive literature pertaining to normal and abnormal exfoliative cytology of many anatomic regions,[5] but the cytology of oral tissues is comparatively unexplored. Miller, Soberman, and Stahl[1] and Montgomery[2] reviewed normal cornification, and von Haam[3, 4] found that leukoplakia and carcinoma of the oral mucous membranes produce recognizable cell forms. Pomeranz and Stahl,[6] Silverman, Becks, and Farber,[8] and Sandler and Stahl[7] concluded that oral neoplasms can be detected by means of exfoliative cytology.

Since August, 1956, the exfoliative cytology of oral lesions has been under study at the Brooklyn Veterans Administration Hospital. In the course of routine oral examination, scrapings were taken directly from any oral or oropharyngeal lesions of leukoplakia, ulceration, granulation, hypertrophy or induration, whether or not carcinoma was suspected. Scrapings were also taken routinely from patients who had been previously treated for carcinoma wherever there were signs of slow healing, ulceration, granulation, or from areas of suspected recurrence. Whenever warranted by clinical signs or history, biopsy specimens were also obtained shortly after the smear. When exudates were available they were smeared. The slides were fixed and stained as recommended

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by Papanicolaou,[5] and were read by two individuals (H.C.S. and S.S.S.), one of whom did not see the clinical lesions. The biopsy specimens were processed and the findings reported by the Pathology Section of the hospital several days to a week after the smears had been read and the smear findings had been recorded.

FINDINGS

Scrapings were taken from oral, oropharyngeal, or neck lesions of 256 patients. Of these, biopsies were not considered necessary in 144 cases (Fig. 1), and 11 patients were too ill, had known metastatic disease, or died before biopsy could be obtained.

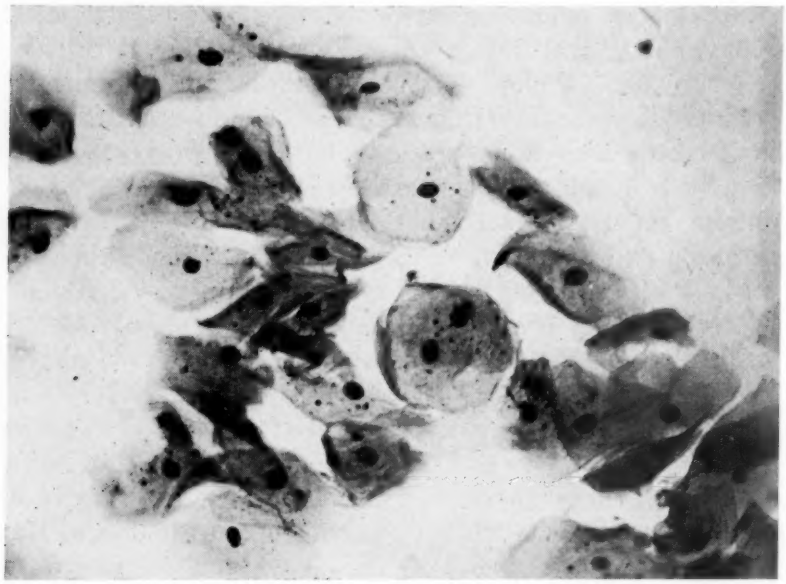

Fig. 1.—Photomicrograph of exfoliated epithelial cells taken from normal buccal mucosa. (Papanicolaou method; ×420, reduced ⅙.)

In the 2-year period, there were 101 patients who provided both a smear and a subsequent biopsy. The relationship between the exfoliative cytology and biopsy findings with respect to carcinoma is shown in Table I. It will be

TABLE I. EXFOLIATIVE CYTOLOGY AND BIOPSY FINDINGS FROM ORAL AND OROPHARYNGEAL LESIONS IN 101 PATIENTS (AUGUST, 1956, THROUGH SEPTEMBER, 1958)

EXFOLIATIVE CYTOLOGY FINDINGS	BIOPSY FINDINGS		TOTAL
	CARCINOMA	NOT CARCINOMA	
Aberrant cells suggestive of carcinoma	64*	3	67
Normal	5	29	34
Total	69	32	101

Chi square (with Yates correction) = 62; P = <0.0005.

*The biopsies of 2 of the patients from this group were reported as negative on first specimen taken. However, in view of the cytologic findings, repeat biopsies were taken and found to be positive.

noted that malignancy was suspected from the cytologic specimen, and confirmed by biopsy in 64 cases; and that malignancy could not be detected by either cytology or biopsy in 29 cases. This constitutes an agreement of 92 ± 2.7 per cent. Aberrant cells suggestive of malignancy were found on three smears but the findings were not confirmed by biopsy. In 5 cases no aberrant cells

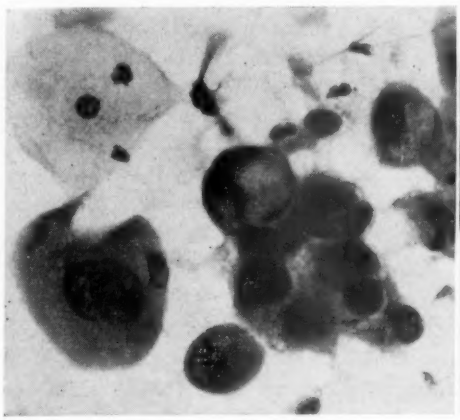

Fig. 2.

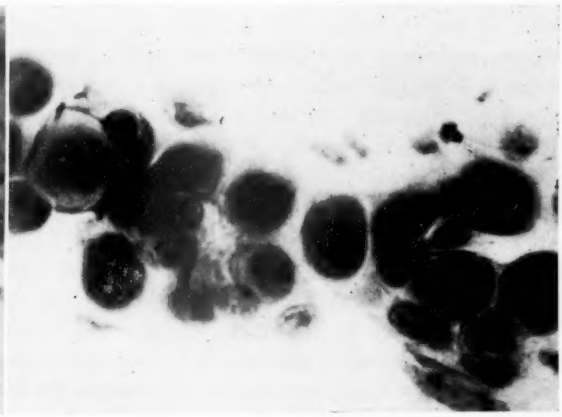

Fig. 3.

Fig. 2.—Photomicrograph of aberrant epithelial cells from scrapings of carcinoma of the tongue. There is one normal cell in the upper left corner. Note enlargement of nuclei reversal of nuclear cytoplasmic ratio, hyperchromasia, clumping with loss of distinct cellular outline, anisonucleosis, anisocytosis, and multinucleation. (Papanicolaou method; ×420, reduced ⅙.)

Fig. 3.—Photomicrograph of atypical epithelial cells suggestive of malignancy from carcinoma of the floor of the mouth. (Papanicolaou method; ×420, reduced ⅙.)

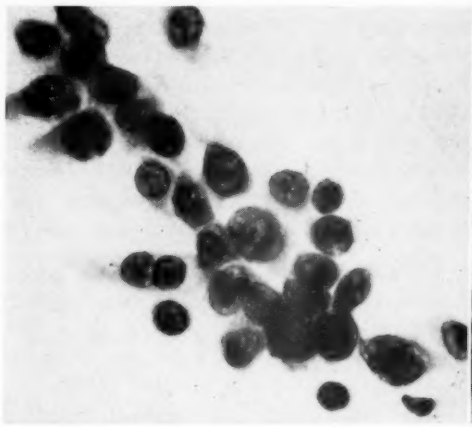

Fig. 4.

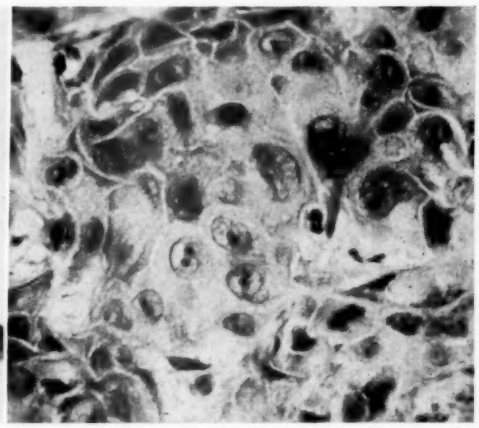

Fig. 5.

Fig. 4.—Photomicrograph of aberrant cells from scrapings of carcinoma of the buccal mucosa. (Papanicolaou method; ×420, reduced ⅙.)

Fig. 5.—Photomicrograph of biopsy specimen from lesion of the buccal mucosa. This is the same area from which the exfoliated cells shown in Fig. 4 were taken. (Hematoxylin and eosin; ×420, reduced ⅙.)

were found but biopsy did demonstrate the presence of carcinoma. It is of particular interest that in 2 of the cases, in which the cytologic findings were consistently suggestive of carcinoma, the first biopsies were negative and repeat biopsies proved to be carcinoma. Figs. 2 through 5 represent some of the cellular abnormalities suggestive of malignant changes.

CASE REPORTS

Clinical Applications.—The clinical usefulness of cytologic examination of scrapings and exudates in the detection and treatment of head and neck cancer is illustrated by the following abbreviated case reports.

CASE 1.—J. M., a 62-year-old white man, was admitted for treatment of Laennec's cirrhosis. Routine oral examination revealed an apparently inflammatory process covering most of the posterior hard palate, soft palate, and the right anterior pillar. On palpation, the tissues were soft, and there was no cervical lymphadenopathy. Neoplasm was not suspected, but a smear from the area revealed cellular abnormalities suggestive of malignancy. Following this finding, a biopsy was taken of the soft palate, which was reported as "inflammatory tissue." A second smear still showed aberrant epithelial cells. Accordingly, a second biopsy was taken from a different area, and this was reported "squamous cell carcinoma." Radiation therapy was instituted and there has been no evidence of recurrence after 2 years.

CASE 2.—J. R., a 70-year-old white man, was admitted because of a mass in the neck of 6 weeks' duration. There were numerous firm, enlarged lymph nodes suggestive of metastatic carcinoma in the right upper deep cervical chain. Careful and repeated examination of the mouth, pharynx, and nasopharynx revealed no evidence of a primary tumor. Blind biopsies of the nasopharynx showed no carcinoma. Smears were taken in the oral cavity and also from the posterior oropharynx. Those taken from the mouth showed only normal cells, but the ones taken from the posterior oropharynx revealed abnormal cells suggestive of malignancy. Biopsy of a neck node showed squamous cell carcinoma. It was assumed that a cryptic primary lesion was present in the nasopharynx and in support of this, x-ray films of the base of the skull demonstrated bony erosion. Radiation therapy was given to the nasopharynx and to the cervical metastases.

CASE 3.—C. T., a 55-year-old white man, was first admitted for recurrence of an adenocarcinoma of the maxillary sinus, treated elsewhere by limited surgery 3 years previously. Resection of the maxilla, palate, and the contents of the right orbit was carried out. A satisfactory prosthesis was constructed, and the patient returned to his normal occupation. After 3 years of regular observation, he was again admitted for evaluation of low back pain. There was no apparent recurrence in the operative area but an erosion resembling granulation tissue was seen on the medial aspect of the orbit. Exfoliative cytology from this area showed aberrant cells and a subsequent biopsy confirmed recurrence of the carcinoma. The low back pain was demonstrated by x-ray film to be due to spinal metastasis.

CASE 4.—J. N., a 77-year-old white man, had been treated over an 8-year period for multiple carcinomas arising from different anatomic sites. These included adenocarcinoma of the rectum, squamous cell carcinoma of the skin of the nose, palate, tongue, and anterior pillar. Each site was treated as it appeared by surgical excision, or by radiation. Close follow-up was maintained because of the tendency of the patient to develop recurrences or new primary lesions. In the course of one routine examination, a smear was taken from the site of previous disease in the region of the anterior pillar. The clinical appearance was not suggestive of carcinoma, but exfoliative cytology revealed numerous abnormal cells. Subsequent biopsy demonstrated recurrence of squamous cell carcinoma.

CASE 5.—O. I., a 37-year-old white man, gave a history of carcinoma of the nasopharynx treated by radiation therapy 2 years before admission. There was recurrence of the lesion in the nasopharynx, and bilateral metastases to the cervical lymph nodes. The primary lesion was treated by external radiation and radium pack. After the primary lesion had disappeared and negative biopsies had been obtained, two radical neck dissections were performed and involved nodes were found bilaterally. Six months later, a bloody mucous discharge was noted in the posterior pharynx. Clinical examination of the nasopharynx showed no abnormalities except a small bleeding point, which did not appear significant.

Smears of the discharge, however, revealed many cells suggestive of malignancy. Subsequent biopsy of the site of bleeding demonstrated the presence of persistent carcinoma. Further treatment was immediately instituted.

CASE 6.—A. P., a 70-year-old white man, was admitted with a fracture of the hip. Pneumonectomy for bronchogenic carcinoma had been performed 2 years previously. Examination revealed a squamous cell carcinoma of the alveolar process of the right mandible. The diagnosis was confirmed by biopsy, and radiation therapy was given with a good result. Six months later, an erosion, 2 mm. in diameter, was noted at the original tumor site. A smear taken of this area demonstrated aberrant cells and subsequent biopsy showed recurrent carcinoma. The erosion was easily healed with further radiation.

CASE 7.—J. V., a 56-year-old white man, was admitted with a large carcinoma of the tongue and floor of the mouth. Involved cervical nodes were present on the homolateral side. A radical neck dissection, hemiglossectomy, and hemimandibulectomy in continuity, was carried out. Within 2 months, enlarged nodes appeared on the other side, and a second neck dissection was performed. Following this procedure, the wound failed to heal at one point, and there was persistent drainage. The exudate was examined for exfoliated cells, and abnormal forms suggestive of malignancy were detected. A biopsy was taken and revealed carcinoma. Radiation therapy was instituted with good immediate results.

CASE 8.—J. D., a 70-year-old white man, presented with a carcinoma of the floor of the mouth and metastatic lymph nodes. Radical neck dissection, hemimandibulectomy, and partial glossectomy was carried out in continuity. Six months later, a draining sinus tract appeared in the submaxillary area. There was no sign of recurrent carcinoma in the oral cavity. No mass was present in the submaxillary triangle and there was no evidence on which to base a suspicion of recurrent carcinoma. The fluid from the tract was examined, and many aberrant epithelial cells suggestive of neoplasm were seen. The sinus tract was then opened and biopsies demonstrated squamous cell carcinoma. Radiation therapy was promptly instituted.

CASE 9.—T. D., a 62-year-old white man, was admitted because of a painful mass on the left side of the neck of 4 weeks' duration. A firm tumor, 4 by 5 cm. in size, was present below the angle of the mandible. The initial examinations for a possible primary site revealed no tumor. A Silverman needle biopsy of the neck mass was then done. The pathology report on the material obtained was "acute and chronic inflammation." Two days following the needle biopsy, a small amount of serosanguineous fluid was noted coming from the site of the puncture. This material was examined and malignant cells were found. The search for a primary site was continued and a very small carcinoma was found on the laryngeal side of the epiglottis.

COMMENT

Exfoliative cytology as a screening technique has proved useful when the appearance of a primary tumor is not very suggestive of malignancy. It is particularly valuable for the early detection of certain carcinomas of the soft palate (Case 1) which assume the appearance of an inflammatory process, but may be quite widespread with a very superficial erosion and no feeling of induration to the palpating finger (Case 1). The finding of abnormal cells in the smear forces the clinician to take repeated biopsies if required, until the histologic diagnosis of carcinoma is proved.

Cryptic primary lesions of the nasopharynx are not uncommon (Case 2) and both clinical examination and blind biopsies may fail to yield a positive diagnosis. In such a case, the finding of aberrant cells in the smears lends additional support to other evidence indicating the location of the primary tumor.

Perhaps the most valuable clinical application of exfoliative cytology is in the postoperative follow-up of patients treated for carcinoma. Local recurrence of carcinoma in the oral cavity is frequent. If a recurrence can be detected at an early stage, additional treatment can be carried out, either for palliation, or to prolong the period of survival of the patient. It has become a routine practice in this clinic to obtain smears from the area of the original primary tumor in all postoperative patients. In some, there may be a small focus of disease which resembles granulation tissue, and the finding of aberrant cells in a smear impels the clinician to take repeated biopsies to verify the diagnosis. In almost all such cases, the biopsy has supported the evidence obtained on the smear, and the diagnosis of recurrent carcinoma has been established at the earliest possible moment. The use of the smear technique for early diagnosis of recurrence of the primary tumor is illustrated by Cases 3, 4, 5, and 6.

Another interesting application of the exfoliative cytology technique was discovered when it was used for the investigation of material obtained from draining sinus tracts, which occasionally appear in the neck following surgery for carcinoma. These tracts are most often caused by infection associated with foreign bodies, such as suture material. However, at times, the exudate may be due to residual or recurring tumor. In the period before a palpable tumor mass makes its appearance, biopsy of the sinus tract may be delayed on the assumption that the cause is an inflammatory process. Cases 7 and 8 are included to demonstrate the use of exfoliative cytology for the early evaluation of sinus tracts caused by persistent carcinoma. Case 9 is of interest because, even though a needle biopsy of a mass in the neck failed to yield a diagnosis of carcinoma, the serum draining from the needle puncture was readily shown to be loaded with aberrant cells.

SUMMARY AND CONCLUSIONS

1. Exfoliative cytology and biopsies of oral and pharyngeal lesions were evaluated independently with respect to the presence of malignancy. Of 101 cases which provided both a smear and a biopsy from the same area, there was agreement between the two techniques in 92 per cent. This would seem to indicate that smears taken from oral and pharyngeal lesions and examined for exfoliated cells provide reliable evidence of cancer.

2. The clinical value of exfoliative cytology applied to diagnosis and treatment of head and neck cancer has been demonstrated for: (a) screening and detection of malignant lesions of innocent appearance, (b) early identification of recurrent carcinoma in the area of the primary tumor in the follow-up of treated malignancy, and (c) the detection of residual tumor in draining sinus tracts following neck dissection.

3. Exfoliative cytology is not a substitute for biopsy. However, when aberrant cells are observed in a smear, the likelihood of the presence of carcinoma is so great that biopsy is mandatory and, if the initial biopsy does not confirm the diagnosis, further repeated biopsies are required.

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TOTALLY DENERVATED POUCHES OF GASTRIC MUCOSA

Method and Preliminary Observations

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IT IS generally accepted at the present time that the gastric antrum secretes a hormone (gastrin) which provokes the secretion of hydrochloric acid from the corpus mucosa. Gastrin is released in response to a wide variety of stimuli applied topically to the antral mucosa, including mechanical distention, meat extract, and acetylcholine. Although it is easily demonstrated that gastrin release continues following division of all extrinsic vagal innervation of the stomach, there is a good deal of evidence suggesting that a local or intrinsic nerve reflex, presumably located in the stomach wall, is essential. For example, it has been shown that both topical anesthetics applied to the gastric antrum and atropine injected parenterally block the release of gastrin by normally effective stimuli, such as meat extract and distention, but do not markedly alter the effectiveness of acetylcholine in releasing gastrin.[5, 8, 9]

Nerve cells are located in two collections in the stomach wall: the myenteric plexus of Auerbach and the submucous plexus of Meissner. In studying the influence of this intrinsic innervation upon the gastric mucosa, various experimental surgical techniques have been used in an attempt to denervate the mucosa. The myenteric plexus may be removed by dissecting the muscular tissue away from the mucosal and submucosal layers.[2, 4, 10] However, to our knowledge a reliable method has not yet been reported for effectively separating the gastric epithelium from the influences of the submucosal plexus of Meissner. Such a method, if it still allowed the epithelial cells of the mucosa to function normally, should afford the possibility of determining to what extent the postulated local nerve reflex is involved in the formation and release of gastrin from the antrum. The purpose of this paper is to report an experimental technique which is believed to achieve the desired result.

METHOD

The essential feature of the experimental technique is the construction of a composite pouch consisting of a pedicled jejunal segment from which the mucosa is removed and replaced with a free, split-thickness graft of gastric mucosa, containing only epithelial elements and lamina propria. An appropriate portion of stomach (either corpus or antrum) is excised and the mucosal-submucosal layer is dissected off the muscularis through the submucosal

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cleavage plane (Fig. 1, *A*). The mucosal-submucosal layer is then stretched smoothly on a padded board and a thin graft cut from the surface using a Brown electrodermatome (Fig. 1, *B*). The graft is cut at a thickness of 0.012 to 0.014 inch and of such a size that it will fit on a previously prepared bed of jejunal muscularis (usually 4 by 15 cm.). This bed is prepared by isolating a 15 cm. segment of proximal jejunum with its attached blood supply, opening it longitudinally along the antimesenteric border and carefully stripping off all

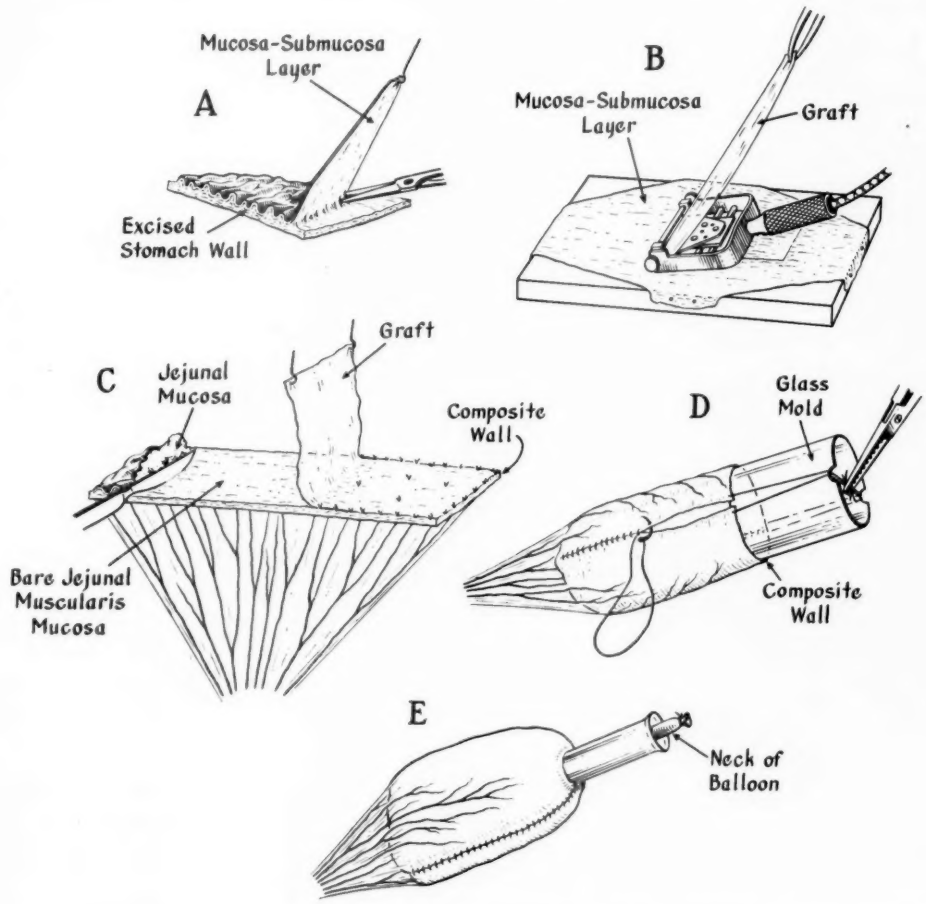


Fig. 1.—Essential steps in preparing the composite gastric mucosa-jejunal muscularis pouch. *A*, Dissection of gastric mucosa-submucosa from muscularis of excised portion of stomach. *B*, Cutting split-thickness graft of mucosa from the mucosa-submucosa layer. *C*, Placing graft on jejunal segment (right side) after removing jejunal mucosa (left side). *D*, Fashioning the pouch. *E*, Completed composite pouch.

jejunal mucosa at the muscularis mucosa (Fig. 1, *C*, left end). After hemostasis is obtained by pressure with moist gauze packs, the graft is placed on the bed and fixed in place with interrupted, fine catgut sutures (Fig. 1, *C*, right end). The composite gastric mucosa-jejunal muscularis structure is then fashioned into a small pouch by folding it end-to-end over a glass mold and suturing together the contiguous free edges at each side with continuous fine silk suture (Fig. 1, *D*). The mold is then carefully removed and replaced immediately by a small balloon which is partially inflated while the open end of

the pouch is closed around a small stainless steel cannula. The balloon is then further inflated with enough air (usually 50 c.c.) to maintain firm pressure on the graft (Fig. 1, *E*). A conventional Heidenhain pouch is also constructed in each animal. The resultant situation in the preparations with corpus mucosa grafts is shown diagrammatically in Fig. 2. The two cannulae are brought through stab wounds in each flank and both pouches are sutured to the parietal peritoneum.

PROCEDURE

Operations were performed on a total of 19 animals divided into three groups as follow: The first group of 7 dogs was operated upon while perfecting the technique. In these animals the composite pouches contained grafts of corpus mucosa to provide a means of proving that the grafted mucosa functioned by observing the secretion of free acid. The second group contained 9 animals in which the composite pouches were lined with grafts of gastric antrum mucosa. A final group of 3 dogs to serve as controls had jejunal pouches constructed in exactly the same manner as the composite pouches, except that no grafts were placed after removing the jejunal mucosa.

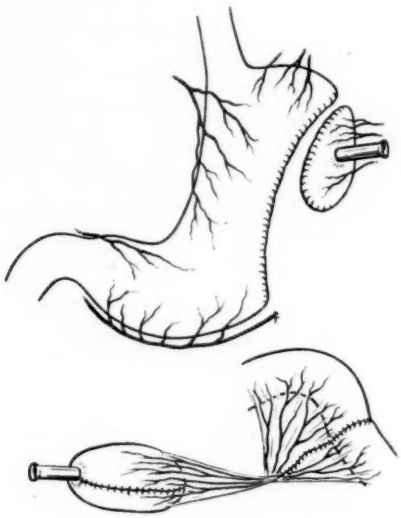


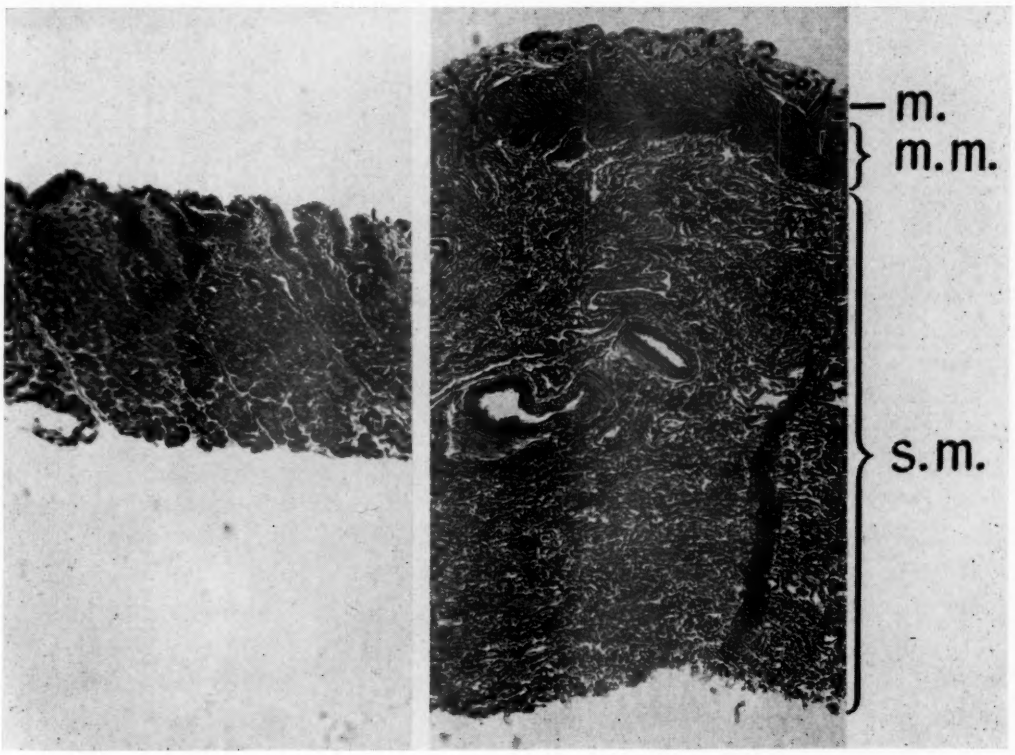
Fig. 2.—Experimental preparation with corpus mucosa graft. Preparations with antral mucosa grafts are the same except a portion of antrum is excised to provide the graft.

Postoperatively, the animals were fasted for 2 days, were fed milk and water only for 2 additional days, and thereafter were given regular kennel ration as desired. All dogs received parenteral antibiotics for 4 days and the pouch was gently, but thoroughly, irrigated once daily wtih warm saline for 5 to 7 days. This irrigation was found to be important for the prevention of small abscesses which tended to form in the pouch until the nonviable portion of the graft had sloughed and regeneration had begun.

At the time of operation, appropriate tissues were preserved for histologic study to insure that the graft was indeed split-thickness (Fig. 3) and that

stripping had removed all jejunal mucosa. In the first two groups periodic biopsies were taken of the grafted pouches which, together with autopsy specimens at varying intervals, provided a chronologic demonstration of the fate of the grafts (Figs. 4 and 5).

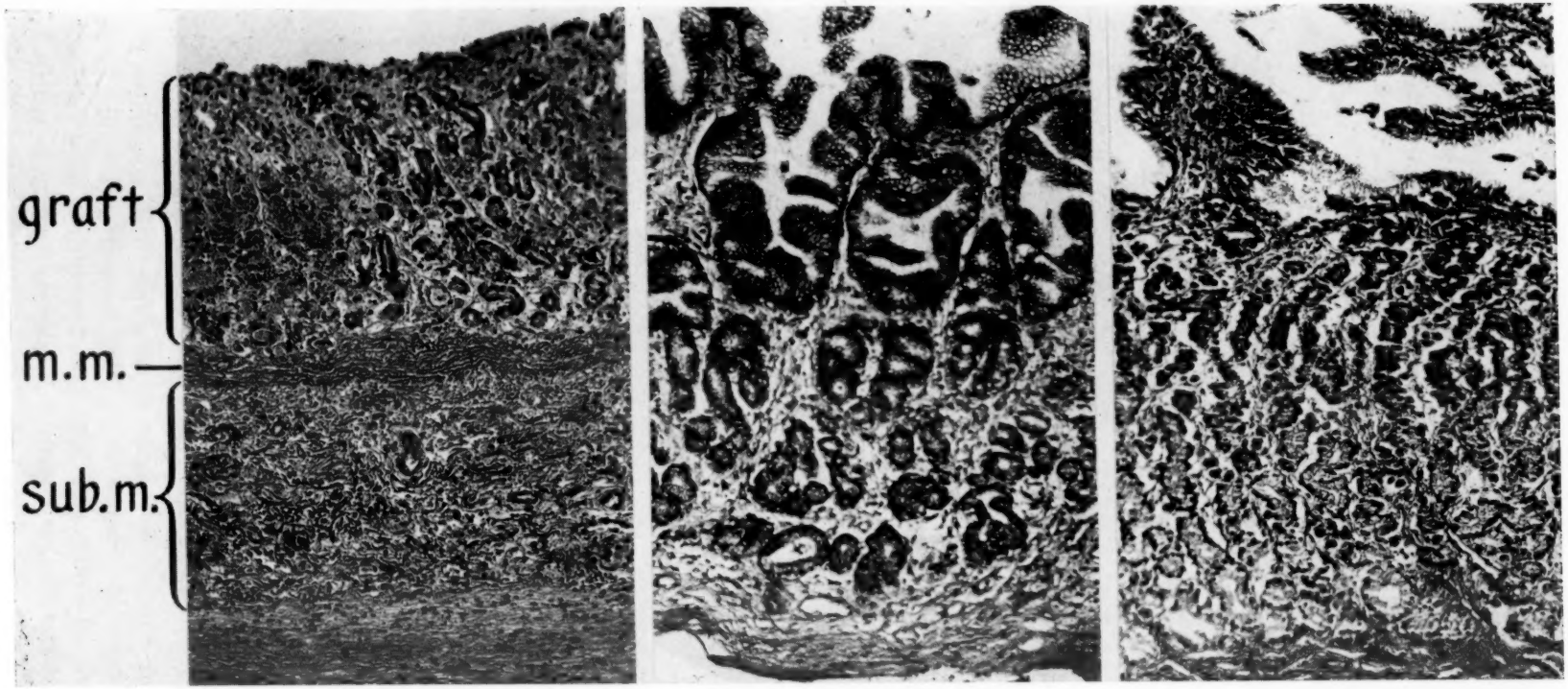
Animals in the first group (corpus mucosa grafts) surviving long enough to be studied were stimulated at approximately monthly intervals with continuous intravenous histamine administered by means of a constant injection apparatus at a rate of 1.7 mcg. per kilogram per minute. Daily pouch secretions were collected from both pouches by means of balloons attached to the cannulae. Surviving animals in the second group (grafts of antral mucosa)



A. *B.*

Fig. 3.—*A*, Split-thickness graft of gastric corpus mucosa. *B*, Remaining portion of corpus mucosa-submucosa layer after the graft has been cut. Note the relatively large amount of submucosa (*s.m.*) which accompanied the mucosa as it was removed by sharp dissection. A thin layer of mucosa (*m.*) remains above the muscularis mucosa (*m.m.*).

were tested at regular intervals by perfusing the composite pouches with a 20 per cent solution of commercial meat extract. Daily collections also were made of pouch secretions. In the 3 dogs with pouches of stripped jejunum but no grafts, biopsies and autopsy specimens were obtained in a manner similar to that for the other animals. Meat extract perfusions of these pouches were performed as in the second group and daily pouch secretions were collected. Free acid was measured by titration with 0.1 N sodium hydroxide using Toepfer's reagent as the indicator.



A. *B.* *C.*

Fig. 4.—Survival and regeneration of transplanted corpus mucosa in composite pouch. *A*, Autopsy specimen 3 days after transplantation showing the partially necrotic graft at the top with an island of surviving gastric glands. The muscularis mucosa, submucosa, and circular muscle of the jejunum are well demonstrated. *B*, Biopsy of mucosa 6 weeks after transplantation. *C*, Autopsy specimen 10 months after transplantation. Arrangement of the glands is a little disorganized, but the glands and cell types appear essentially normal.

RESULTS

Composite Pouches Lined With Corpus Mucosa.—Three animals survived 6, 9, and 10 months in apparent good health. Four other dogs died at various intervals during the first 5 postoperative days, one from a technical error, the others apparently in part from factors associated with the length and extent of the operation. Later the procedure was performed in two stages, since which there have been no operative deaths.

Histologic study of the composite pouches from the animals dying in the early postoperative period revealed survival of a considerable portion of the glands in the deepest layer of the graft and occasional areas in which the entire thickness appeared to have survived the transplantation. A representative section, taken at this time, as well as a biopsy taken later in the course of the experiment and at autopsy, are shown in Fig. 4. It is seen that the surviving glandular elements rather rapidly regenerate a layer of gastric mucosa, containing all the usual cell types, which eventually is remarkably normal in appearance.

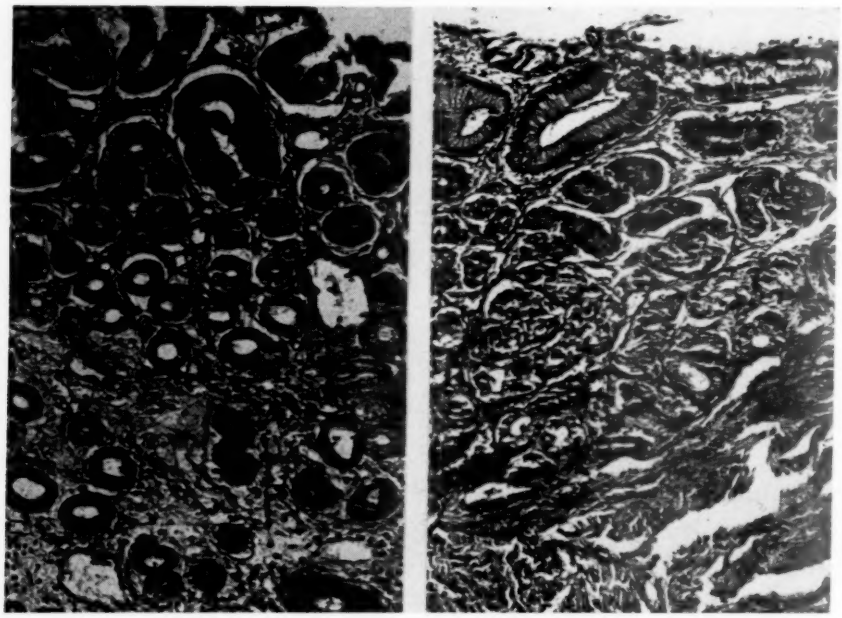
Of the 3 survivors in the first group, the composite pouch of one gave a positive response to histamine stimulation at 6 weeks after operation. The secretions changed from scanty alkaline mucus to clear, watery gastric juice within 10 minutes of starting the histamine infusion. The volumes were small, 4 c.c. per hour, but contained 80 clinical units of free hydrochloric acid. This secretion was maintained at a steady rate for 2 hours while the histamine was continued, then promptly diminished to only a drop or two of mucus with an alkaline reaction when the infusion was stopped. Three subsequent similar tests in this animal at varying intervals up to 6 months, postoperatively, all gave essentially the same result. The daily collections of pouch secretions averaged about 20 c.c. of mucoid material with no free acid for the first 6 weeks, after which the volumes increased slightly and free acid was present. From the third to the sixth month, the daily collection averaged 30 c.c. in volume with up to 5 mEq. of free hydrochloric acid.

At autopsy after 6 months the composite pouch in this animal was soft and pliable with a clean, smooth, velvety lining which on microscopic section had the appearance of essentially normal corpus mucosa, as shown in Fig. 4, *C*.

The other 2 animals in the first group had daily secretions from the composite pouches ranging from 10 to 30 c.c. of definitely mucoid material, which, however, was grossly contaminated with a seropurulent drainage related to chronic abscess formation around their cannulae. This daily secretion never contained free acid, but the pouch with the less severe infection did respond, on two occasions, to histamine stimulation in a manner similar to the first dog. At autopsy the pouches of these latter dogs were smaller than that of the first, a little scarred with the mucosa being somewhat patchy although, where present, it was grossly and microscopically indistinguishable from that of the first dog.

Composite Pouches Lined With Antral Mucosa.—Two animals in this group died in the immediate postoperative period and one sloughed the graft

on the fourth day. This was the only complete failure of the grafting technique. The 6 surviving animals of this group remained in good health for many months. A total of 20 perfusions of the grafted pouches with 20 per cent meat extract solution failed to produce stimulation of secretion from the Heidenhain pouches in every instance save one where a questionable response was obtained. Daily secretions from the grafted pouches averaged 10 to 20 c.c. of fairly clean mucus. Serial biopsies demonstrated survival and rapid regeneration of normal-appearing pyloric glands, and autopsies in 5 of the animals revealed pouches lined with clean, grossly normal, smooth mucosa which appeared essentially normal microscopically (Fig. 5) in four instances. In the remaining specimen, the histologic examination showed it readily recognizable as antral mucosa but the appearance was more irregular and disordered than in the other cases. The sixth animal is still alive.



A. *B.*

Fig. 5.—Survival and regeneration of antral mucosa graft. *A*, Biopsy 3 weeks after transplantation. Surface epithelium at the top with regenerating glands in the deeper portions. *B*, Autopsy specimen 5 months after transplantation. Surface epithelium at the top, jejunal submucosa at the bottom. Well-formed, essentially normal appearing pyloric glands may be seen, despite some postmortem changes.

Control Pouches.—In the third group of 3 dogs with control pouches of bare jejunal muscularis, the pouches all scarred down to small, dense clumps of granulation tissue within 2 weeks. Perfusion of these pouches with meat extract produced no response from the Heidenhain pouches and daily collections of secretions amounted to only a few cubic centimeters of serosanguineous exudate, never mucoid in character. Careful study of microscopic sections, prepared at the time of autopsy after about 2 months, revealed only chronic inflammatory reaction and scarring with a rare collection of a small number of cells here and there which perhaps represent a few persisting jejunal glands.

DISCUSSION

The objective of this experiment was to devise a method to separate gastric mucosa from all nervous influences while preserving actual mucosal cell function intact, and there is good reason to believe that this has been accomplished. Previous attempts to achieve this goal have frequently made use of indirect, pharmacologic methods of paralyzing or inhibiting nervous elements, but this approach is objectionable in that the widespread systemic action of such agents makes it difficult to evaluate alterations in function observed in individual organs or tissues. Surgical denervation has also been carried out by various techniques,[3, 4] none of which may reasonably be assumed to remove completely all of the intrinsic nerve supply. The usual dissection or stripping techniques for separating mucosa from the muscularis unquestionably remove the influence, if any, of the myenteric (Auerbach's) plexus and probably disrupt some of the connections between mucosa and the deepest portion of the submucosal plexus. However, it may be shown that a considerable portion of the latter plexus persists in its usual relationship to the mucosa (Fig. 3, *B*), and the assumption seems justified that these intimately located neurons very likely play a part in any local reflex which might be present. In order to assume that any such mucosal preparation is completely free of influence from the intrinsic innervation, the mucosa must be separated anatomically from all the intrinsic nerve supply.

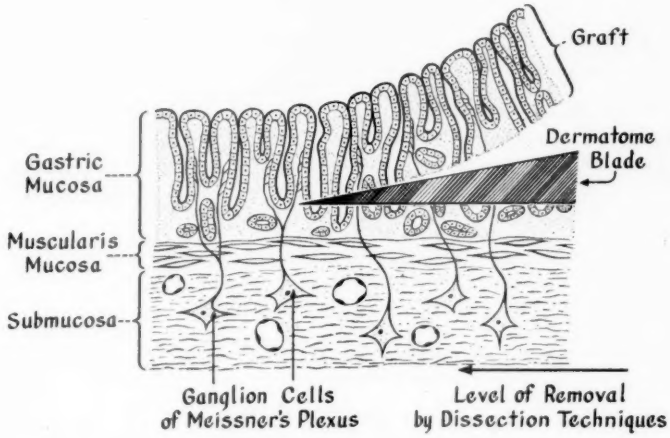


Fig. 6.—Diagrammatic representation of relationships of the graft to mucosa-submucosa layer. Note that removal of mucosa by dissection leaves a large portion of submucosa with its contained ganglion cells attached to the mucosa and that the graft is cut definitely superficial to the muscularis mucosa.

The grafting technique described in this paper removes only epithelial elements (and a small amount of associated lamina propria) at a level definitely superficial to submucosa (Fig. 6) thus insuring that no portion of Meissner's plexus is transplanted with the graft. It is demonstrable (Fig. 3) that anatomically the grafts are indeed devoid of any submucosa when transplanted and that they can survive and regenerate in a foreign location. The first part of the objective is therefore successfully fulfilled.

Whether the independent function of such transplanted mucosa is unchanged is more difficult to resolve. We have seen that normal-appearing glandular elements survive and rather rapidly regenerate a mucosal layer which is remarkably similar to the original tissue. Unchanged morphology in this situation by no means guarantees unchanged function, but it certainly argues in favor of it. Studies by Ferguson[1] and more recently by Longmire[7] show that canine gastric mucosa regenerates rapidly and completely and functions normally after considerable trauma, including attempted complete removal by scraping. These experiments strongly support the proposal that transplanted and regenerated mucosa may be considered normal in this respect.

More direct evidence for normal function of the grafted mucosa was obtained in the present experiments by showing that the parietal cells in grafted corpus mucosa can respond, at least qualitatively, to standard secretory stimuli, both artificial (histamine injection) and normal (mediated through the animal's antrum in response to daily feedings). The decreased responses in 2 of the 3 animals studied in this manner may be explained on the basis of a relatively small area of mucosa in the presence of an inflammatory exudate which neutralized free hydrochloric acid and probably inhibited secretion. The technical problems responsible for this contamination have been resolved in animals operated upon later in the series. The present experiments would seem to provide additional direct evidence to support previous investigations done with atropinized and cocainized corpus mucosa which demonstrated the independent function of parietal cells in response to humoral stimuli.

It must be pointed out that the grafted mucosa may not remain completely denervated even though all original nervous connections have been divided. Sympathetic innervation very likely accompanies the revascularization of the graft, and the possibility exists that postganglionic parasympathetic fibers from the jejunal submucosa may similarly invade the graft. Whether these fibers could make functional connections with surviving end organs in the mucosa is questionable but very difficult to disprove. This problem is being investigated at present. Is a local neuron reflex through Meissner's plexus necessary for the production or release of gastrin by the pyloric antrum? The preliminary study reported here suggests that apparently normal antral mucosa completely separated from the influence of the submucosal nerve plexus fails to respond to what ordinarily is a potent chemical stimulus to gastrin release. More extensive investigations along these lines are necessary to corroborate this evidence and to locate more precisely the site of formation and the mechanism of release of the hormone. Such experiments are being carried out at present. It is felt that the method herein described for totally denervating gastric mucosa will prove useful in future investigations of this problem.

SUMMARY

1. A method is described for preparing pouches containing gastric mucosa which is believed to be completely devoid of any extrinsic or intrinsic innervation. The technique entails the transplantation of split-thickness grafts of gastric mucosa containing only epithelial elements and lamina propria.

2. Grafts transplanted by this method from either the antrum or corpus of the stomach can survive and regenerate to essentially normal-appearing mucosa on microscopic sections.

3. Preliminary observations indicate that transplanted totally denervated mucosa from the body of the stomach is able to secrete free hydrochloric acid in response to appropriate stimuli, whereas transplanted, totally denervated mucosa from the gastric antrum does not secrete gastrin in response to a normally potent natural stimulus (meat extract).

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THE MANAGEMENT OF THE ULCER-BEARING PORTION OF THE DUODENUM DURING SUBTOTAL GASTRECTOMY

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A LARGE proportion of the serious early postoperative complications of gastrectomy for duodenal ulcer are directly related to the technical problems encountered in the management of the ulcer-bearing portion of the duodenum. Blowout of the duodenal stump secondary to inadequate closure or to devascularization following extensive resection, duodenal fistula formation secondary to leakage from the stump, pancreatitis secondary to resection of a deeply penetrating ulcer, pancreatic fistula secondary to pancreatic necrosis or direct duct trauma, and encroachment upon or trauma to the common bile duct with resultant obstructive jaundice or biliary fistula formation are responsible for much of the morbidity and mortality following gastrectomy. The possibility of these complications poses a challenge to every surgeon who discovers a deeply penetrating duodenal ulcer or an ulcer which extends far down toward the second portion of the duodenum. An immediate decision must be reached whether to remove the ulcer-bearing portion of the duodenum or to leave it in situ.

Many surgeons have taken the position that all duodenal ulcers can and should be removed when subtotal gastrectomy is the operation of choice. There is, however, another group of surgeons who practice ulcer removal along with subtotal gastrectomy when it is technically easy to perform but who leave the ulcer in situ when its removal might make duodenal closure difficult or might endanger the substance or ducts of the pancreas, or might encroach too closely upon the region of the common bile duct.

Until recently, it had been taught that removal of the offending duodenal ulcer was an essential part of surgical cure. However, results from newer operations have cast great doubt on the necessity for ulcer extirpation as an essential part of cure, even in actively bleeding cases. There are many clinics reporting good results with simple vagotomy, vagotomy plus gastrojejunostomy, or vagotomy plus pyloroplasty. Adherents of these methods of surgical treatment do not remove the duodenal ulcer and, in a recent communication from Smith and Farris,[1] they report that they merely ligate the bleeding ulcer bed prior to performing a vagotomy and pyloroplasty. In a series of 150 patients so treated, there were no deaths and excellent results were said to have been obtained in over 90 per cent of cases.

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It has long been the practice of the senior author to remove the ulcer-bearing portion of the duodenum only when it can be performed safely, without increasing too greatly the technical hazards of the operation. If ulcer removal appears to be dangerous, resection is performed proximally through the duodenum or even by transecting proximal to the pyloric sphincter. If the stomach has been cut across above the pyloric sphincter, all of the pyloric mucosa is reamed out down to the duodenum.[2] Before performing either of these maneuvers in cases of active bleeding, the duodenum is opened on its anterior surface and the base of the ulcer is ligated in order to obtain hemostasis.

The practice of leaving the ulcer in situ in certain cases has been predicated upon the belief that ulcer removal is not an essential step in the attainment of a good result. It has been felt that complete diversion of the gastrointestinal stream from the ulcer surface, and the performance of a 75 to 80 per cent gastrectomy to remove the acid-producing mucosa are the basic elements essential to surgical cure. Observation of large numbers of patients over long periods of time postoperatively demonstrates that a duodenal ulcer left in situ after gastrectomy rarely remains active, causes symptoms, or bleeds.

In order to re-evaluate the question of ulcer removal versus nonremoval, the last 300 cases of subtotal gastrectomy for duodenal ulcer which were performed at the Jewish Hospital of Brooklyn were studied. These operations were done by thirty members of the attending staff and ten supervised members of the resident staff. No attempt was made to select cases.

This study concerns itself with a comparison of the immediate postoperative complications and mortality in those cases in which the duodenal ulcer was removed and those cases in which the ulcer was left in situ. If only a portion of an ulcer or an edge of the ulcer crater was found in the resected specimen, it was recorded as an "ulcer removed." Even when the gross or microscopic specimen showed only a superficial ulcer or erosion, it was recorded as a resected ulcer. In all instances, the pathologic findings, not the surgical operative report, were used as the determining factor as to whether the ulcer or part of the ulcer had actually been removed.

FINDINGS

In the series of 300 cases, the duodenal ulcer was removed in 119 (39.7 per cent) instances and was left in situ in 181 (60.3 per cent) instances. There were 13 serious postoperative complications (10.9 per cent) among the 119 patients who had undergone ulcer resection. There were 12 serious postoperative complications (6.6 per cent) among the 181 patients who had undergone no ulcer resection. There were 8 postoperative deaths (6.7 per cent) among the 119 patients who had undergone ulcer resection. There were 2 postoperative deaths (1.1 per cent) among the 181 patients who had undergone no ulcer resection.

Of the 13 complications which ensued in the group in which the ulcer was removed, there were 3 instances of acute pancreatitis and 1 case of pancreatic fistula, 3 cases of duodenal fistula, 3 cases of wound dehiscence, 2 instances of

irreversible postoperative shock, and 1 case of renal failure (Table I). Eight of these complications resulted in death. The 3 patients who developed pancreatitis died, one of the 3 who developed a duodenal fistula died, the patient who formed a pancreatic fistula succumbed, and the remaining three mortalities occurred in those who developed irreversible shock and renal failure. It is interesting to note that 7 of these 8 deaths can be related directly to the extensive nature of the operative procedure and to the unusual trauma which accompanied the mobilization and removal of the ulcer-bearing portion of the duodenum.

TABLE I. COMPLICATIONS IN CASES IN WHICH DUODENAL ULCER WAS RESECTED*

CASE NUMBER	AGE†	SEX	NATURE OF COMPLICATION	OUTCOME OF COMPLICATION
397749	62	M	Wound dehiscence	Recovered
397192	60	M	Duodenal fistula	Recovered
391050	50	M	Pancreatitis	Died
392759	51	M	Pancreatitis	Died
397701	48	M	Renal failure	Died
379709	72	F	Irreversible surgical shock	Died
388653	48	M	Wound dehiscence	Recovered
389446	64	M	Pancreatitis	Died
378006	57	M	Wound dehiscence	Recovered
377673	56	M	Irreversible surgical shock	Died
401769	52	M	Duodenal fistula	Died
414794	68	M	Pancreatic fistula	Died
413178	65	M	Duodenal fistula	Recovered

*Nine of these patients were operated upon by the attending staff and 4 patients were operated upon by the resident staff under the direct supervision of an attending surgeon.
†Average age: 58 years.

TABLE II. COMPLICATIONS IN CASES IN WHICH DUODENAL ULCER WAS NOT RESECTED*

CASE NUMBER	AGE†	SEX	NATURE OF COMPLICATION	OUTCOME OF COMPLICATION
390580	41	M	Wound dehiscence	Recovered
397248	60	M	Wound dehiscence	Recovered
378213	72	M	Multiple pulmonary emboli	Recovered
383389	54	M	Pancreatitis	Recovered
377241	56	M	Cardiac failure	Died
375544	31	M	Duodenal fistula	Recovered
375452	41	M	Pancreatic fistula	Recovered
353334	51	M	Jejunal fistula	Recovered
403274	56	M	Subhepatic abscess	Recovered
402075	74	M	Postoperative hepatitis	Died
398684	68	F	Wound dehiscence	Recovered
430074	62	F	Pancreatic fistula	Recovered

*Eight of these patients were operated upon by the attending staff and 4 patients were operated upon by the resident staff under the direct supervision of an attending surgeon.
†Average age: 55.6 years.

Of the 12 complications which followed in cases where the duodenal ulcer was left in situ, there were 2 instances of pancreatic fistula, 1 case of jejunal fistula, 1 case of duodenal fistula, and 1 case of pancreatitis. The other 7 complications in this group were not related to the manner in which the ulcer-bearing portion of the duodenum was treated surgically. These latter complications consisted of 3 cases of wound dehiscence, 1 case of subhepatic abscess formation, 1 case of multiple pulmonary emboli, 1 case of cardiac failure,

and 1 case of postoperative hepatitis (Table II). It is interesting to note that the 2 patients who died in this group of complications, namely, the patient with cardiac failure and the patient with postoperative hepatitis, did not succumb from conditions which were related to the method of handling the ulcer-bearing portion of the duodenum.

COMMENT

In studying the foregoing data, it is not unwarranted to presume that several of the complications and deaths might have been avoided if the ulcer had been left in situ. One cannot help but observe that not a single patient among the 181 in whom the ulcer was left in situ died as a result of disruption of the duodenal stump, duodenal fistula, pancreatitis, pancreatic fistula, common bile duct injury, irreversible postoperative shock, or postoperative hemorrhage. On the other hand, 7 of the 8 deaths which occurred among the 119 patients whose duodenal ulcer was resected were caused by one of the above-mentioned complications. The question arises, therefore, as to the advisability of removing a complicated duodenal ulcer. Clinical experience demonstrates to our complete satisfaction that excluded ulcers left behind in the duodenum rarely remain active, perforate, or bleed. Certainly the latter complication can be averted in almost all cases by ligation of the ulcer bed prior to closing the duodenal stump. Furthermore, the prime objectives of subtotal gastrectomy for ulcer which are to exclude the vulnerable duodenal mucosa from the constant bathing of gastric juice and to remove sufficient stomach so as to produce a permanent hypochlorhydria or achlorhydria, are obtained whether or not the duodenal ulcer is resected. Finally, the ulcer which has been left in situ has no bearing upon the development of late complications of ulcer surgery such as the formation of a marginal gastrojejunal ulcer, the dumping syndrome, persistent anemia, bilious regurgitation, chronic underweight, or diarrhea.

CONCLUSIONS

1. A duodenal ulcer should be resected in those patients submitted to subtotal gastrectomy when such removal will not significantly increase the incidence of complications such as duodenal stump blowout or disruption, duodenal fistula, pancreatitis, pancreatic fistula, common bile duct injury, or irreversible postoperative shock.

2. Statistical analysis of 300 cases of subtotal gastrectomy for duodenal ulcer shows that the above-enumerated complications occur 60 per cent more often in those cases in which the ulcer-bearing portion of the duodenum has been resected.

3. Complications occurring in cases in which the ulcer has been left in situ are less severe, less often terminate in death, and are less likely to be related to the surgical method of handling the duodenum than in those cases in which resection has included the ulcer-bearing portion of the duodenum.

4. The operative mortality in the group in which the ulcer had been resected was 6.7 per cent whereas it was only 1.1 per cent in the group of cases in which the ulcer had been left in situ. This would indicate that it is preferable not to resect the ulcer-bearing portion of the duodenum when the ulcer penetrates very deeply into the pancreas, when duodenal closure after resection might be very complicated, or when the ulcer is in close anatomic proximity to the common bile duct.

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UPPER GASTRIC TRANSECTION (TANNER OPERATION)

Its Failure to Control Varical Bleeding

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In 1950, Norman Tanner of London introduced a new operative procedure which was designed to curb bleeding from esophagogastric varices.[5] This operation, which he labeled "porto-azygos disconnexion," consists in transection and re-anastomosis of the upper portion of the stomach. Its rationale stems from the premise that venous drainage from structures inferior to the diaphragm fill the esophageal varices. Interruption of this afferent collateral pathway should permit varical collapse.

Tanner initially transected the stomach in its mid-portion and included division of the vasa brevia and branches of the left gastric vein. Recurrent bleeding followed this technique in 3 out of 4 of his patients and prompted him to modify the procedure to a subcardiac transection. "By an abdominothoracic approach the lower 5 cm. of the oesophagus, the cardia, the upper 5 cm. of greater and lesser curve of the stomach are entirely freed from all external vascular connexions. The stomach is then completely transected 5 cm. below the cardia and firmly resutured."[6]

Initially designed as an operation for extra- or subhepatic portal hypertension, Tanner now recommends its use both as an emergency and as an interval maneuver for the control of varical bleeding due to cirrhosis. Although acknowledging the value of portacaval shunt in eliminating recurrent varical bleeding, he believes the risk of encephalopathy following shunt operations to be formidable.

Unfortunately, precise information of Tanner's total results and experience is not available. Unquestionably, he has treated many patients in this manner, but he has not accurately recorded the number, the mortality, or the incidence of recurrent bleeding. Nevertheless, in his most recent publication in 1958,[3] he states that the operation has been used ". . . on many cases with excellent long term effects." Reference is specifically made to 11 patients treated by this operation during acute varical bleeding. Hemorrhage was initially controlled in each case, but later recurrent bleeding developed in 3. These 11 patients probably include the 8 patients referred to in 1954, 3 of whom had recurrent bleeding.

In this country, recorded experience with upper gastric transection is limited. Allen[1] utilized this procedure in 5 patients during acute varical bleeding. Two of the 3 patients in whom this operation alone was used died

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postoperatively. In the other 2 patients, splenorenal shunt was added. Both of these patients survived, but one died 10 months later in hepatic decompensation. Acute bleeding was controlled in all 5 patients. In a recent personal communication, Allen relates successful use of this operation in 2 additional patients. Nevertheless, he wishes to withhold final judgment on its value until more evidence is available. McCorkle[3] used this procedure to control successfully acute varical bleeding which developed in a young woman immediately post partum. During an 8-month follow-up, bleeding did not recur in this patient. In contrast, utilizing a procedure which is basically similar to the Tanner operation, Wangensteen encountered recurrent varical bleeding after 90 per cent distal gastrectomy[9] and as a result of this experience has given up this operation.[8]

Our interest in this operation was stimulated by our dissatisfaction with other procedures designed to eliminate bleeding in extrahepatic portal hypertension. In this disease, a venous shunt is usually precluded by major portal tree occlusion. Accordingly, we were distressed by the magnitude and undesirable postoperative sequelae of esophagogastric resection and by the undependability of transesophageal varical ligation. Furthermore, the premise upon which the Tanner operation was based appeared logical. However, the dismaying results encountered in the 8 patients to be reported here have prompted not only this report but our abandonment of this operation. A brief outline of the pertinent details of the case histories of these 8 patients follows.

CASE REPORTS

CASE 1.—A 66-year-old woman with extrahepatic portal hypertension, secondary to portal vein occlusion following previous cholecystectomy, had upper gastric transection and splenic artery ligation performed electively on March 11, 1955. Bleeding from proved esophageal varices had occurred on two previous occasions. Gastric transection was performed at approximately the junction of the upper and middle thirds of the stomach. Two months postoperatively, while at home, she suddenly and unexpectedly died. Necropsy was not permitted. Postoperatively, x-ray examination of the esophagus had not been obtained. Bleeding had not recurred and was not associated with her death.

CASE 2.—A 57-year-old woman with cirrhosis had upper gastric transection performed on June 15, 1955, as an emergency procedure to control persistent bleeding from proved esophagogastric varices. Gastric transection was carried out at approximately the junction of the upper and middle thirds of the stomach. Postoperatively, bleeding continued intermittently for 3 weeks. During the ensuing year she bled profusely on four occasions. Persistent varices were demonstrated. Portacaval shunt was performed in September, 1956. There has been no further bleeding since that time and the patient continues to do well.

CASE 3.—A 68-year-old woman with extrahepatic portal hypertension, secondary to portal vein occlusion following previous cholecystectomy, had upper gastric transection performed electively on June 7, 1956. Bleeding from proved esophagogastric varices had occurred on seven previous occasions. Gastric transection was performed 3 cm. below the cardia after mobilization of the lower esophagus and upper stomach and division of all neighboring vascular connections. Twenty days after surgery, severe bleeding recurred and, during the 2½ years since upper gastric transection, hospitalization has been required four times for massive varical bleeding. Persistent varices have been demonstrated. The patient refuses further surgery.

CASE 4.—A 3½-year-old boy with extrahepatic portal hypertension, secondary to portal vein occlusion from an unknown cause, had upper gastric transection, vagotomy, and pyloroplasty performed electively on March 19, 1957. Bleeding from proved esophagogastric varices had occurred on three previous occasions. Gastric transection was performed 3 cm. below the cardia after mobilization of the lower esophagus and upper stomach and division of all neighboring vascular connections. Ten days postoperatively, persisting esophageal varices were demonstrated on x-ray examination. During the 7 months that followed surgery and before he was lost to further follow-up, severe bleeding occurred on two occasions; the first occurred 4 months postoperatively.

CASE 5.—A 3½-year-old girl with extrahepatic portal hypertension, secondary to portal vein occlusion from an unknown cause, had upper gastric transection, vagotomy, and pyloroplasty performed electively on April 9, 1957. Bleeding from proved varices had occurred once previously. Gastric transection was performed 3 cm. below the cardia after mobilization of the lower esophagus and upper stomach and division of all neighboring vascular connections. Eleven months later massive bleeding recurred and large varices were demonstrated. On March 25, 1958, segmental esophagogastrectomy with jejunal segment interposition was performed. Six months later varices were once again demonstrable and 2 months after this massive bleeding recurred once more.

CASE 6.—A 40-year-old woman with cirrhosis and extrahepatic portal hypertension, secondary to portal vein occlusion due to previous splenectomy and attempted portacaval shunt, had upper gastric transection, vagotomy, and pyloroplasty performed electively on June 17, 1957. Bleeding from proved esophagogastric varices had occurred on thirteen previous occasions. Gastric transection was performed 3 cm. below the cardia after mobilization of the lower esophagus and upper stomach and division of all neighboring vascular connections. Two months after surgery, x-ray examination of the esophagus revealed varices unchanged in size from those demonstrated preoperatively. Eleven months postoperatively severe bleeding recurred. On Aug. 5, 1958, segmental esophagogastrectomy with interposition of a segment of transverse colon was carried out. Her course since this operation has been complicated by marked nutritional problems.

CASE 7.—A 12-year-old girl with cirrhosis had upper gastric transection performed on Aug. 9, 1957, as an emergency procedure to control persistent bleeding from proved esophagogastric varices. Gastric transection was performed at approximately the junction of the upper and middle thirds of the stomach. Postoperatively, bleeding continued unabatedly and death occurred 15 days later, primarily due to the effects of prolonged hemorrhage.

CASE 8.—A 1-year-old female infant with extrahepatic portal hypertension, secondary to portal vein occlusion due probably to omphalitis after birth, had upper gastric transection, vagotomy, pyloroplasty, and splenectomy performed electively on Sept. 7, 1957. Gastric transection was carried out 3 cm. below the cardia, after mobilization of the lower esophagus and upper stomach and division of all neighboring vascular connections. On the second postoperative day moderate bleeding recurred. Five months later severe bleeding recurred from proved esophagogastric varices. On Feb. 20, 1958, segmental esophagogastrectomy was performed. The infant failed to recover completely from this operation and died 2 months later, primarily from the effects of continuing sepsis.

COMMENT

Portal hypertension in 5 of the 8 patients reported herein was extrahepatic, in 2 it was secondary to cirrhosis, and in one it was a combination of the two. In the 2 patients with cirrhosis, the operation was carried out as an emergency procedure during acute varical bleeding. In the other 6 patients the operation was performed electively, 3 to 33 days after the last bleeding episode.

One patient, Case 1, died suddenly and unexpectedly 2 months postoperatively. Necropsy was not obtained. Gastrointestinal bleeding had not recurred and a follow-up x-ray examination of the esophagus had not been obtained. This case clearly does not permit pertinent evaluation of the efficacy of the Tanner operation. However, an analysis of the other 7 cases enjoins the conclusion that this operation cannot be relied upon to eliminate varical bleeding (Table I). In each of these patients, massive bleeding either continued or recurred after the operation.

TABLE I. PERTINENT DATA OF RESULTS OF UPPER GASTRIC TRANSECTION (TANNER OPERATION) IN 8 PATIENTS WITH BLEEDING ESOPHAGOGASTRIC VARICES

CASE NUMBER	TANNER OPERATION PERFORMED AS AN EMERGENCY OR AS ELECTIVE PROCEDURE	POST-OPERATIVE BLEEDING	INTERVAL FROM OPERATION TO FIRST POST-OPERATIVE BLEEDING	NUMBER OF POST-OPERATIVE BLEEDING EPISODES	POSTOPERATIVE VARICES DEMONSTRATED	COMMENT
1	Elective	No	—	—	—	Patient died suddenly and unexpectedly 2 months postoperatively from unrelated cause
2	Emergency	Yes	Immediate	5	Yes	Subsequently had portacaval shunt; no further bleeding
3	Elective	Yes	20 days	5	Yes	Refuses further surgery
4	Elective	Yes	4 months	2	Yes	Lost to follow-up
5	Elective	Yes	11 months	2	Yes	Subsequent esophagogastrectomy; varices still demonstrable and has bled once more
6	Elective	Yes	11 months	1	Yes	Subsequent esophagogastrectomy
7	Emergency	Yes	Immediate	1	Yes	Died 15 days postoperatively with continued bleeding
8	Elective	Yes	2 days	2	Yes	Subsequent esophagogastrectomy; died 2 months after this operation from sepsis

In both of the cirrhotic patients, Cases 2 and 7, who were subjected to emergency gastric transection, bleeding continued postoperatively and its severity appeared not to have been significantly influenced by the operation. Balloon tamponade was required immediately postoperatively and several times thereafter in both. One of them died 15 days after surgery, primarily from the effects of prolonged hemorrhage. The other continued to bleed intermittently for 3 weeks after surgery. During the ensuing year, this patient

bled four more times and x-ray examination revealed persisting esophageal varices. A portacaval shunt was then performed. There has been no further bleeding during the 2½ years that have followed this procedure. In contrast to the experience reported by others, gastric transection proved valueless as a method for emergency control of acute varical bleeding in these 2 patients.

Improvement in the capacity of gastric transection to control interval bleeding in extrahepatic portal hypertension, for that matter, is not seen when the remaining 5 cases are evaluated. Severe bleeding recurred in all 5. The longest postoperative period of freedom from hemorrhage was 11 months, and one patient bled briefly just 2 days after surgery. In all cases, recurrent or persisting esophageal varices were demonstrated by x-ray examination, esophagoscopy, or by both procedures. In one case, varices unchanged in size from those seen preoperatively were demonstrated as early as 10 days after surgery. A brief résumé of the dismal course followed by these 5 patients is appropriate. One patient, Case 3, has bled five times since her operation which was performed in June, 1956. She refuses further surgery. Another, Case 4, bled two times following surgery and was then lost to follow-up. Because of recurrent hemorrhage, the remaining 3 patients (Cases 5, 6, and 8) were subsequently subjected to extensive esophagogastrectomy with or without enteric interposition. All of these have fared poorly after this operation also. One died 2 months later from complications of sepsis. Another demonstrated recurrent esophageal varices within 6 months and severe recurrent varical bleeding within 8 months. The third patient has troublesome nutritional problems although neither varices nor bleeding has developed during the 3 months that have elapsed since esophagogastrectomy.

It is difficult for us to relate these uniformly dismal results of gastric transection with the satisfactory results reported by others. In accord with Tanner's own poor results with mid-gastric transection, it is acknowledged that an ideal transection was not accomplished in 3 of the 8 patients herein reported. In each of these 3, transection was performed at a level approximating the junction of the upper and middle thirds of the stomach. In the remaining 5 patients, however, the criticism that a technically inadequate operation had been performed cannot be maintained. In each of these 5 patients, the lower segment of esophagus and the upper one-half of the stomach were completely mobilized and freed of all vascular connections. Vagotomy and pyloroplasty were added to transection of the stomach at a level approximately 3 to 4 cm. below the cardia. This procedure, similarly, failed to prevent recurrent varical hemorrhage in a single patient.

The total experience related here compels us to retract an earlier, tentative recommendation which we made for this operation.[4] Further, we are highly suspicious that at present there does not exist a satisfactory operative procedure for the management of varical bleeding in a patient in whom a venous shunt cannot be constructed. Esophagogastrectomy in 8 of our patients has almost uniformly been complicated by disabling nutritional problems, esophagitis, or recurrent varical bleeding. Although Crile's[2] experience

has been good, transesophageal varical ligation in 5 of our patients has been successful in only one. The other 4 all bled again and 3 have died primarily as a result of hemorrhage. Furthermore, it is readily apparent that we cannot concur in Tanner's recommendation that gastric transection be extended to include its use as an interval operation for patients with bleeding varices secondary to cirrhosis. In these patients, a decompressing venous shunt can be performed with the anticipation that recurrent varical bleeding will be infrequent. The complication of periodic encephalopathy, which may occur after portal decompression, is recognized. This hazard, however, is rather uncommon and its likelihood must be balanced against the probable ineffectiveness of gastric transection in eliminating varical bleeding.

SUMMARY

The pertinent feature of the case histories of 8 patients in whom a Tanner operation was performed have been presented. One patient does not contribute to an analysis of the effectiveness of the operation in eliminating varical bleeding. From an analysis of the remaining 7 patients, however, this operation must be considered to have failed in its purpose. Massive varical bleeding either continued or recurred in all 7. From this data, we are obliged to reach the conclusion that the Tanner operation, in our hands at least, is useless in the management of varical bleeding in either extrahepatic or intrahepatic portal hypertension, performed either as an emergency or as an interval procedure.

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THE SURGEON'S TACTICS IN THE TREATMENT OF ACUTE CHOLECYSTITIS

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THE problem of treating acute cholecystitis is one of the most vital problems of abdominal surgeons. Although the number of patients operated upon in connection with acute cholecystitis is growing from year to year, still there does not exist any uniform opinion on the indications for the surgical treatment of acute cholecystitis, as well as on the choice of a suitable method of anesthetization. This conflict of opinion found its expression in the communications of a number of surgeons at the Sixth Plenary Session of the Board of the All-Union Surgical Society in November, 1956, devoted to the problem of acute cholecystitis (A. T. Lidsky, A. I. Miranov, V. I. Struchkov, S. P. Protopopov, T. P. Makarenko, and others[5]).

Until recently many surgeons avoided surgical intervention during attacks of acute cholecystitis, since a high rate of mortality was observed after operations performed under such conditions. This circumstance compelled the surgeons to resort to operative treatment only in cases when the inflammatory process showed a steady growth, often accompanied by the destruction and perforation of the wall of the gall bladder and by the development of peritonitis.

It is quite natural that the performance of operations in the presence of the afore-mentioned complications leads in numerous cases to a lethal outcome.

In acute cholecystitis, at the stage of destruction, the inflammatory process is not confined to the gall bladder, but, as shown by investigations carried out in our clinic by Dr. E. M. Perkin,[3] it also affects the parenchyma of the liver, the biliary tract, the pancreas, and other organs.

According to summary data published by Professor A. I. Mironov[5] concerning postoperative mortality recorded in 25 hospitals of Moscow in the period between 1951 and 1954, of 2,505 patients operated upon in connection with acute cholecystitis 275 died; thus, the mortality rate was 11 per cent. In individual hospitals the percentage of postoperative mortality varied from 7.75 to 19.5 per cent.

On the basis of the material studied, Professor A. I. Mironov concluded that postoperative mortality in acute cholecystitis is mainly due to tardy application of the patients for medical advice as well as to their belated hospitalization for surgical treatment. The direct basic cause of the patients' death is peritonitis accompanied by cardiovascular insufficiency and pneumonia. J. Seneque, Marcel Roux, and M. Nicol[6] investigated 50 patients

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suffering from stones in the common bile duct; they observed these patients in the period between 1935 and 1950 in Hotel Dieu. The disease was accompanied by different complications in individual patients, by high temperature and jaundice. All the patients were operated upon; 12 of them died after the operation, a mortality rate of 24 per cent. Of these 12 patients, one died from an injury to the vena porta, and the remaining 11 from liver insufficiency. The authors arrived at the conclusion that an early operation must be considered as the method of choice.

Analyzing their material relating to the surgical treatment of acute cholecystitis, Pines and Rabinovitch[4] point out that the prognosis is better when the interval between the attack of the disease and the operation is shorter. Thirty of their patients were hospitalized shortly after an attack of the disease but were operated upon within a period of 3 to 27 days after admission. The mortality rate was 20 per cent.

The age of patients suffering from concomitant grave diseases is of essential significance for the prognosis. In elderly patients the application of general narcosis considerably impedes the operation. Deranged liver function in such patients and profound intoxication, particularly in old and obese persons, often suffering from various cardiovascular and other disorders, necessitate the application of a sparing method of anesthetization, a method which will in no way contribute to the intensification of the toxicosis.

At the Clinic of the Second Chair of Clinical Surgery at the Central Institute for Improvement of Physicians (for a long time headed by Professor A. V. Vishnevsky,[9] creator of local infiltration anesthesia in the U.S.S.R.) local procaine anesthesia is used in acute cholecystitis. Unlike ether narcosis, procaine does not produce any intoxication and does not exert any noxious influence on the liver. It is simple, convenient, and facilitates the operative technique by preparing the tissues hydraulically, which is of particular importance in conditions of deranged topographoanatomic relationships. A consecutive and thorough accomplishment of each stage of anesthetization is an indispensable condition for the success of the operation; local anesthesia must always precede each stage of the operation and the operative technique must be highly delicate.

Our clinic has been applying local anesthesia in operations on the biliary tract since 1934, that is, for 25 years. I take the liberty of dwelling here, in brief, on separate stages of local anesthesia as it is applied in our clinic. Before the operation begins we perform a right-side paranephric procaine blockade. Only then do we proceed to anesthetize the peritoneal wall. The skin, the subcutaneous fatty tissue, the muscles, and the extraperitoneal fatty tissue are subjected to anesthesia in direct succession. After incising the tissues of the abdominal wall, we introduce additionally a solution of procaine into the extraperitoneal fatty tissue from the inside of the abdominal cavity. Then the procaine solution is introduced into the root of the mesentery of the liver angle of the large intestine (flexura hepatica) beneath the lower edge of the duodenum, from whence the fluid spreads into the splanchnic region. Finally

the procaine solution is introduced under the peritoneum covering the hepatoduodenal ligament. Now, beginning with this ligament, subject, of course, to the absence of any destructive changes in its wall, only then (and by no means earlier) is it possible to start investigating the state of the gall bladder and of the biliary tract. As stated earlier, we begin the local anesthesia with the performance of a paranephric blockade. The creeping infiltrate deposited in the retroperitoneal space constitutes, as it were, a basis for subsequent anesthesia.

At present many authors regard local procaine anesthesia not only as an anesthetizing factor, but also as a factor normalizing the trophic function of the nervous system and favorably influencing the course of the inflammatory process (A. V. Vishnevsky,[9] A. D. Speransky,[8] K. I. Parchon,[2] and others). It is generally known that a paranephric procaine block exerts a powerful curative action in acute pancreatitis, calling forth a reverse development of the acute inflammation of the pancreas when it is at the stage of serous saturation (infiltration) of the tissues. A bilateral paranephric procaine blockade in acute cholecystitis likewise favorably changes the course of the inflammatory process unless the disease takes a destructive form. In the latter case the application of a paranephric blockade becomes a factor of differential diagnosis.

Our clinic is of the opinion that patients suffering from acute cholecystitis must be operated upon possibly earlier. This viewpoint, however, requires certain clarification. We do not consider it possible to draw analogies between the indications for the operative treatment of acute cholecystitis and those for the operative treatment of acute appendicitis. When a patient with acute cholecystitis is admitted to the clinic (which often happens at night), the surgeon first of all performs a bilateral paranephric procaine block. Not infrequently soon after the blockade (sometimes within 2 or 3 hours), the inflammatory process shows a tendency to subside. The pains disappear, the temperature returns to normal, the leukocytosis declines, and the local phenomena abate. Subsequently, when all the acute phenomena disappear, the patient is subjected to a thorough and all-round examination in the course of which we apply duodenal probing, perform contrast cholecystography, and ascertain the liver function. After the examination the question of operative treatment in the "cold" period is decided. But if several hours after the application of the blockade the patient does not exhibit any tendency toward a reverse development of the inflammatory process, we deem it expedient to perform the operation within 24 hours after the admission of the patient. During this period, if no pronounced phenomena of hepatitis, cholangitis, and pancreatitis are as yet observed, such patients usually endure the operation perfectly well, with the course of the postoperative period being likewise favorable.

As a rule during the operation we apply cholangiography which was elaborated in our clinic by Dr. E. M. Perkin. Since last year we have also been applying manometry with the help of a special hydromanometer designed in our clinic by Dr. S. A. Zchakaya. The usual methods of examining the

biliary tract during the operation, such as inspection, palpation, and probing, do not always disclose the full picture of the pathologic changes taking place in the biliary tract and in the pancreatic duct; neither do they prevent the surgeon from overlooking stones, scars, and so forth, in the biliary ducts. Of great importance in this respect is the application of manometry and cholangiography during the operation. Our surgical experience has more than once proved the value of applying these two methods of investigation. Manometry enables us to ascertain the presence of the blockade of the biliary ducts when an increase in the "initial pressure," a high "pressure of passing by," and a heightened "residual pressure" manifest themselves. Cholangiography makes it possible to determine the level and cause of the obstruction, the dilatation of the biliary ducts, the passage of the contrast into the liver ducts, and its nonpassage into the duodenum. Cholangiography also reveals the shadows of the concrements and the compression of the ducts by a tumor.

The method of local procaine anesthesia, applied in our clinic, allows us to carry out manometry and cholangiography during the operation, and this does not require the application of any relaxants or hyperventilation.

Claude E. Welch,[10] who thoroughly studied the literature pertaining to this problem refers to the results of cholangiography performed in 110 patients 10 days after the operation. The cholangiograms showed that in 20 per cent of all cases, the common bile duct contained stones which had been overlooked during the operation. The author also has analyzed 100 cases observed by him personally. In all these cases no cholangiography was performed during the operation, but postoperative cholangiography performed 7 to 10 days after the operation revealed in 53 cases the presence of stones in the common bile duct. On the basis of these facts the author concluded that the expediency of applying cholangiography during the operation can in no way be denied; at the same time, however, he rightfully emphasizes that the operating surgeon must constantly perfect his technical skill. J. Gershon-Cohen, S. M. Berger, and V. Kremens,[1] analyzing two methods of cholangiography—one by introducing the contrast per os, the other by introducing it intravenously—point out that until recently the oral method was considered best. However, the application of a new compound—Cholografin—for the purpose of securing adequate contrast has changed the situation. The authors first applied Cholografin postoperatively. Having obtained good results, they began to use it for preoperative cholecystography by introducing it intravenously. The authors state that they applied Cholografin preoperatively in 54 cases; in 48 cases they obtained perfect visualization of the gall bladder. The authors consider this preparation highly effective, practical, and safe.

In the period between November, 1955, and February, 1959 (after the Second Surgical Chair had been attached to Town Clinical Hospital No. 50), 285 patients suffering from acute cholecystitis were operated upon in our clinic. This number does not include patients in whom phenomena of acute pancreatitis were predominating. Nine patients were operated upon in connection with cancer of the biliary tract accompanied by secondary inflammatory phenomena.

The following interesting fact should be stressed. Investigations of 126 histotopographic sections of the removed gall bladder revealed atypical epithelia in 6 cases. In order to perform histologic investigations of the liver tissue, small pieces of the liver were taken during the operation from 22 patients with acute cholecystitis. These investigations carried out in our clinic by Dr. E. M. Perkin[3] revealed, in patients suffering from acute cholecystitis and particularly from acute obstructive jaundice caused by a stone or by a concomitant acute edema of the head of the pancreas, a more or less strongly pronounced picture of adipose dystrophy of the liver cells, edema, and considerable inflammation of the connective tissue. It is noteworthy that in these conditions the gall bladder may have a catarrhal form of inflammation.

In all operations performed by us on patients with acute cholecystitis we applied cholecystectomy.

In cases of difficult cholecystectomies Schein and Hurwitt[7] advise opening the bottom of the gall bladder, removing its contents, and performing further cholecystectomy under the control of a finger introduced into the cavity of the bladder. In our practice there was no need to resort to this kind of interference. We think, however, that the technique proposed by these authors should not be disregarded.

Of the afore-mentioned 285 operations, 274 were performed under local anesthesia and only 11 under ether-oxygen narcosis.

In the postoperative period, prior to the removal of the drainage tube from the common bile duct, we also employed cholangiography extensively, which makes it possible to ascertain the evacuation of bile into the duodenum.

The analysis of our material obtained during the last 3 years shows that grave postoperative complications were extremely rare in the practice of our clinic, while cholemic hemorrhages were not observed at all. We believe that this circumstance is directly dependent on the method of local anesthesia applied in our clinic.

Only 9 patients died postoperatively; thus, the mortality rate was only 3.15 per cent. In 2 cases, the death of the patients was due to ether-oxygen narcosis which caused acute liver insufficiency. Two patients died of peritonitis which had developed prior to the operation. One patient (a woman) died 12 days after the operation of an infarct of the myocardium; another, aged 78 years, died 2 months after the operation of hypernephroma of the right kidney. One of the patients, 61 years old, died one month after the operation of suppurative cholangitis and numerous abscesses of the liver; this patient had been operated upon in a very bad state with phenomena of suppurative cholangitis and obstructive jaundice. The death of a woman of 76 years occurred 5 days after operation owing to cerebral hemorrhage. Finally, one patient died postoperatively of acute cardiac insufficiency; autopsy revealed severe rheumatic changes in the heart.

In conclusion, I should like to make the following observations:

1. Patients suffering from acute cholecystitis must be placed not in medical but in surgical divisions of hospitals and must be under observation of surgeons from the very beginning.

2. The indications for earlier operations in acute cholecystitis must be extended.

3. The application of a bilateral paranephric procaine blockade in acute cholecystitis in some cases proves to be a powerful curative factor—in others, a method of differential diagnosis.

4. The method of choice of anesthetization in acute cholecystitis is local procaine anesthesia according to the method of creeping infiltration introduced by A. V. Vishnevsky.

5. The application of a paranephric procaine blockade, which is an integral component of local anesthesia in acute cholecystitis, fully insures the insensibility of the patients during the operation, serves as a curative factor with regard to concomitant pancreatitis, and eases the patient's postoperative period.

6. The application of cholangiography and manometry during the operation, as well as repetition of cholangiography after the operation, is a reliable method which makes it possible to recognize the presence of disease of the biliary tract and to diagnose the character of the biliary obstruction, as well as a means of establishing the patency of the biliary ducts.

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AN IMPROVED COMMON DUCT DILATOR

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EXPLORING the common duct and dilating the sphincter of Oddi is an everyday procedure, and yet it has some well-known hazards. Of these, making a false passage through the ampullary portion of the common duct by failing to pass a dilator directly through the sphincter itself is probably more common than we know.

Usually a small tip probe, 2 mm. or less, can be worked through the sphincter with a fair degree of certainty. The trouble arises when the larger tip dilators are pushed through against a fair amount of resistance, as one has no real certainty that the larger tip is being directed squarely into and through the sphincter. It can very easily be put through the side of the common duct immediately proximal to the sphincter, and this should be avoided if possible.

To obviate this, Mixter devised a flexible probe that has a small guide tip, followed at spaced intervals along the stem by a series of graduated dilators. I have had no experience with this device, but it seems it might be somewhat awkward to manipulate.

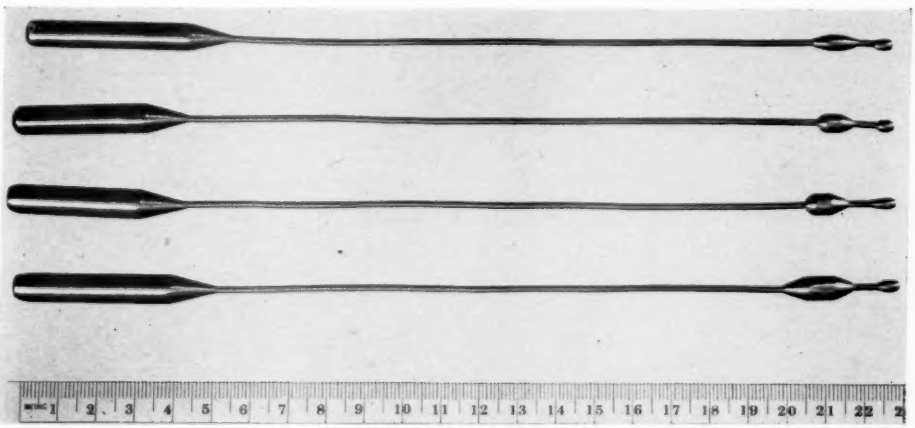

Fig. 1.—Note the same size small guide tip on each probe. Dilators are graduated in size, from 3 to 6 mm.

Bennett[1] recently described his device to ensure that the probe tip has passed through the ampulla. I have not seen this instrument, but it seems to have the deficiency common to all—that is, the small tip is still passed blindly through the ampulla. Once within the duodenal lumen the stream of fluid injected against the anterior duodenal wall confirms the intraduodenal position of the tip, but not necessarily the position of entry of the probe into the duodenal lumen.

The four probe-dilators shown in the illustrations do offer one a little extra margin of safety in dilating the sphincter of Oddi. Each one has a small guide

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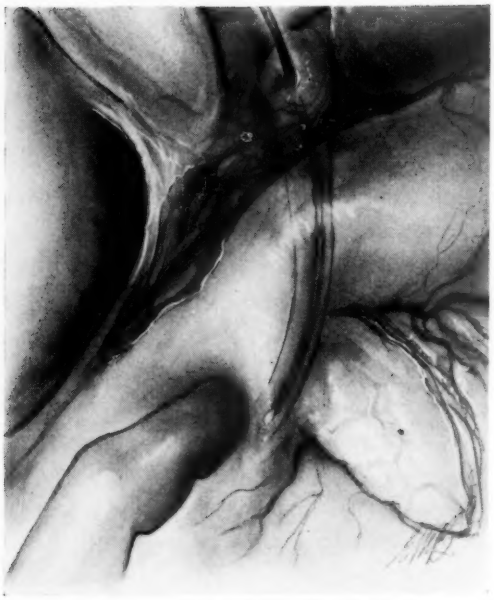

Fig. 2.—Palpating tip of an ordinary small size probe through the anterior duodenal wall. The tip has just passed through the sphincter of Oddi into lumen of the duodenum.

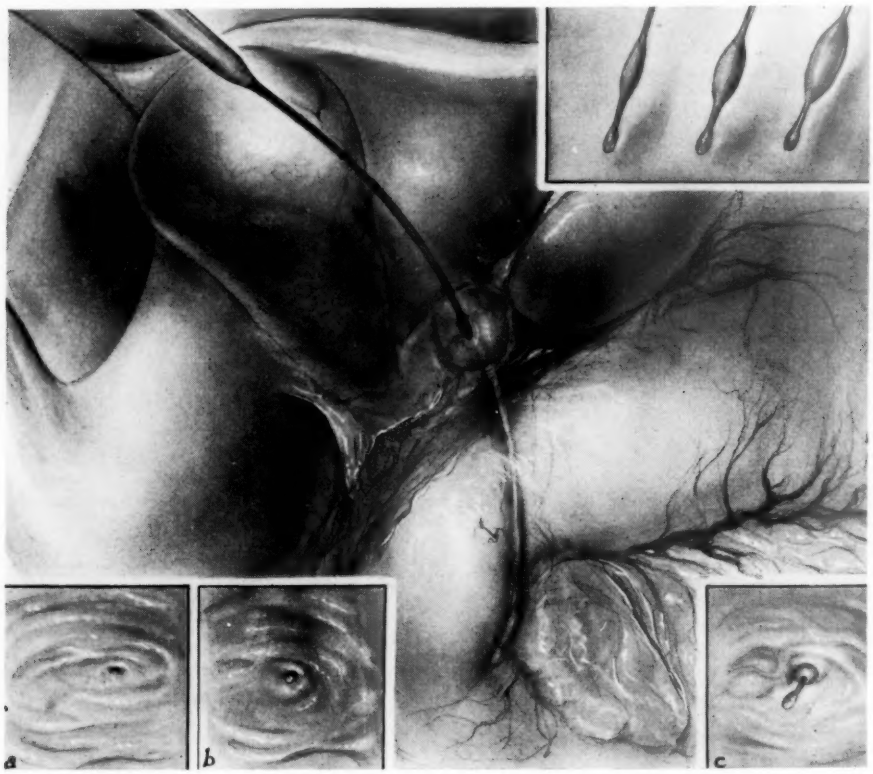

Fig. 3.—The illustration shows small size probe dilator being passed through the common duct, searching forward through the sphincter. *a*, View of papilla opening. *b*, Small tip has passed through opening. *c*. After palpation of small tip through anterior duodenal wall, dilator portion is pushed on through. *Upper right-hand inset,* three graduated probe-dilator tips.

tip of the same size, approximately 2 mm. in diameter. About ¼ to 5/16 of an inch behind each small tip is a larger dilator somewhat cone-shaped on each end, and the dilators increase in size from about 3 mm. to 6 mm. The cone-shaped ends aid in pulling the dilator back through the sphincter as well as pushing it through.

In use, the probe with the smallest dilator, of course, is used first. The little guide tip is passed with the utmost care and gentleness, although at times a certain amount of force must be used. There is usually a very characteristic "snap" as the tip slips through a narrow sphincter, and, unless this is felt, a false passage may have been created.

Actually there are two of these characteristic "snaps" felt when this first probe-dilator is used. The first is noted as the small guide tip goes through the sphincter, the second is felt as the dilator portion is passed. The other size probe-dilators provide only one "snap" which comes as the dilator portion passes through the sphincter, the small tip no longer meeting any resistance. After the small guide tip has passed through the sphincter it is very easy to palpate through the anterior duodenal wall, and one is then reasonably certain that the dilator just behind has to pass through the sphincter as pressure is exerted on it. The distance between the guide tip and the dilator corresponds roughly to the width of the sphincter area. After using the first probe, one inserts the next size dilator, and after again palpating the small guide tip as it emerges through the sphincter one does not hesitate to use sufficient force to push the larger dilator through against perhaps considerable resistance, and with a minimum of risk.

It is true that this is still a blind procedure, and as such involves the same risk that any other similar probing procedure does. This, of course, is the risk that the small tip itself may make a false passage through the common duct rather than go through the sphincter. However, this risk, while not entirely eliminated, is definitely lessened, and to this extent this procedure is somewhat safer. It should be remembered that if one has accidentally made a false passage with the smallest probe dilator, the larger dilators will probably be passed with ease. On the other hand, if the small tip has passed through the sphincter, a fair amount of force will be required to pass the different dilators against the resistance of the narrowed sphincter. A false passage offers little resistance; this may be a useful tip.

I find that dilating the sphincter with these probes can be done with more real assurance and confidence than with any other type with which I am familiar. These probes can be made to any desired specification.* The dimensions shown have proved satisfactory in a limited series. There is one other advantage to a probe of this nature, that is, it is a single instrument and has no small parts to break off or be lost in the manipulation.

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*Manufactured by The Chappell Instrument Co., 2836 Delafield Street, Houston 23, Texas.

THE TREATMENT OF CARCINOMA OF THE ESOPHAGUS

A Comparison of Surgery and X-Ray

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(From the Department of Surgery, Hartford Hospital)

INVOLVEMENT of the esophagus by epidermoid carcinoma continues to be one of the most serious diseases surgeons are called upon to treat. Although the entire length of this organ is subject to excision, it is relatively inaccessible except in its lower most part. In addition, it is in such close contact with irremovable structures that the desirable wide excision can rarely be achieved. The lack of an enveloping serous layer has permitted an earlier dissemination of malignant cells and increased the technical problems of a successful anastomosis. The curious tendency of this carcinoma to show extensive microscopic submucosal extension and even skip areas, leaves the surgeon insecure in his estimate of an adequate margin. Yet the decision to augment his surgical margin may so increase the scope of the surgery that mortality and morbidity figures rise sharply while he gains a centimeter.

In spite of the unfriendly behavior of this lesion, much good has come from the efforts of surgeons to cope with it during the last 15 years. As a result of that experience it seems clear that when the tumor-bearing esophagus can be resected with a good margin and an esophagogastrostomy performed below the aortic arch, we can expect acceptable mortality and morbidity figures and cure rates in line with those of other carcinomas. When, however, the above conditions are not met, there seems to be room for doubt.

A lively controversy has been going on in the medical literature regarding the treatment of esophageal carcinoma. Although Churchill[3] showed, in 1942, that lower esophageal carcinoma could be treated by surgical excision, it was not until 1944 that Garlock[4] and, a little later, Sweet[10] established the feasibility of resection therapy for tumors above that level. A wave of optimism was thereby created because a hitherto largely untreatable group of patients were afforded the possibility of cure or, at the least, a significant degree of palliation. However, there is a growing body of statistical evidence which shows a generally high morbidity and mortality rate for esophageal resection, coupled with a low cure rate; and these figures are most striking for middle and upper esophageal lesions.[5-9] Such figures are discouraging but in dealing with a fatal disease they have little practical significance unless some other form of treatment is available.

One of the most fascinating characteristics of squamous cell carcinoma of the esophagus is its morphologic similarity to carcinoma of the lip. The tumors cannot be distinguished from one another except by virtue of their location.

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X-ray cures over 95 per cent of carcinomas of the lip but until recently has done little for esophageal carcinoma. But even if one grants that cancer of the lip and esophagus are the same tumor, they differ from one another to a marked degree because of their respective locations. Carcinoma of the lip is a surface tumor and x-rays can be applied to it without the loss of strength which occurs with deeply situated tumors. Carcinoma of the esophagus, on the other hand, is one of the deepest tumors in the body. But if a dose of x-ray could be delivered to the esophageal tumor which was equivalent to the dose delivered to the lip tumor, one would expect similar results at least from the standpoint of tumor destruction.

The delivery of a comparable dose to a deep tumor was virtually impossible with older types of therapy. Deleterious effects on skin and lung always forced the radiologist to discontinue treatment before the desired tumor dose was achieved. However, beam-directed therapy at high voltage theoretically makes possible the delivery of enough roentgens to the esophageal tumor to destroy it.

Watson and Brown,[12] in 1951, reported on 12 patients treated with beam-directed 400 kv. x-ray, all of whom had pathologically proved epidermoid carcinoma of the esophagus. Of these, 5 were alive and symptom-free up to 4⅓ years. The remaining 7 died in 3 months to 3 years. Postmortem examinations on 4 of these revealed no remaining esophageal cancer in any of them and distant metastases were found in but one.

Buschke,[1] in January, 1954, compared the results of surgery and radiation in carcinoma of the esophagus and showed a higher survival rate for cervical lesions when x-ray was used, whereas surgery gave the best results with lesions of the lower quarter of the thoracic esophagus. When surgery and x-ray were compared in the treatment of the rest of the thoracic esophagus, the results of radiation were superior; that is, Sweet's 3.3 per cent 5-year survival (1:30) versus 6.2 per cent 5-year survival (8:128) in the cases of Nielson and Smithers.

In 1954, a cobalt^{60} Theratron was acquired by the Hartford Hospital, and its advent, coinciding with some disappointment with the results of surgical treatment, led to an increase in the x-ray treatment of these tumors. At this time then, a group of surgically treated and x-ray treated patients are available for study and is the subject of this report.

SURGICAL GROUP

The original group of cases included all patients with pathologically proved epidermoid carcinoma of the esophagus admitted to the Hartford Hospital in the years 1944 through 1951. There were 74 such patients and the usual diagnostic data are presented without comment in Tables I through V.

Table VI shows the treatment given to this group. The x-ray therapy at that time consisted in 200 kv. without beam direction.

Table VII shows the average survival rate in months for the various types of treatment.

TABLE I

Number of cases	74
Males	4:1
Average age	64.5
Youngest	44
Oldest	85

TABLE II. SYMPTOMS

Duration	1-12 months (average, 4.2 months)
Dysphagia	92 per cent
Weight loss	80 per cent (average, 20 pounds)
Pain	32 per cent
Hoarseness	14 per cent

TABLE III. PHYSICAL FINDINGS

Weight loss	60 per cent
Cervical mass	8 per cent
Abdominal mass	5 per cent

TABLE IV

	X-RAY	ENDOSCOPY
Examinations	65	61
Lesion demonstrated	65	59
Correct interpretation	62	56 (positive biopsy)

TABLE V. LOCATION OF LESION

Upper	16 (22%)
Middle	37 (50%)
Lower	21 (28%)

TABLE VI. TREATMENT

None	19
X-ray	21
Gastrostomy	15
Resection	19

TABLE VII. SURVIVAL (AVERAGE MONTHS) FROM ONSET OF SYMPTOMS

No treatment	7.5
X-ray	11.0
Resection (all)	18.0
Resection (minus postoperative deaths)	25.0

TABLE VIII. SURVIVAL AFTER GASTROSTOMY

Number of cases	15
Less than 1 mo.	7
One to 4 mo.	5
One each	6, 9, and 27 months

TABLE IX. PERCENTAGE DATA

Patients	74 (100.0%)
Explored	33 (44.5%)
Resected	19 (25.7%)
Mortality	7 (36.8%)

Table IX presents operability, resectability, and mortality rates in the surgical group.

Table VIII shows separate survival rates for those patients subjected to gastrostomy.

Finally, Table X gives the detailed survival figures in the resection group.

TABLE X. SURVIVAL AFTER RESECTION IN 19 PATIENTS

7	Operative mortality	Average survival 8 mo.
10	Survived 2 to 34 mo. (average, 13 mo.)	
1	Survived 7 years (distal esophagus)	
1	Survived 6 years (distal esophagus)	

X-RAY GROUP

Since the advent of the Theratron at the Hartford Hospital, 53 patients with carcinoma of the esophagus have been treated with "million volt x-ray." Many of these (a) were terminal, (b) had known metastases, (c) did not complete the full treatment, (d) had adenocarcinoma, or (e) had surgical as well as x-ray therapy. Such cases were not thought to be comparable with the resection group and were eliminated. This left 22 cases for study, all of whom had pathologically proved epidermoid carcinoma. The pertinent facts are listed in Table XI.

TABLE XI

Average age	67 years
Sex	19 male—3 female
Location	Cervical, 5 Mid-thoracic, 16 Lower, 1
X-ray	4,000 to 6,000 r. in 21 to 68 days:rotation
Survival from completion of therapy (0, 1,1,2,2,2,3,3,3,4,5,5,5,10,10,11,13,14,19, 21,27,28 mo.)	1 to 28 mo.; average, 9 mo.
Palliation	Significant symptomatic relief in 18

A special comment must be made about the complications which followed x-ray therapy. The word "followed" was carefully chosen since it is not clear whether they are related to x-ray or a part of the disease itself.

Two patients died of massive hemorrhage shown at post mortem to be due to aortoesophageal fistula and one died of pulmonary infection and a tracheoesophageal fistula. In these cases it is felt that the esophageal tumor had extended into the aorta and trachea and that the terminal event of an open communication was inevitable, although x-ray treatment may have hastened it. Another patient developed activation of an old pulmonary tuberculosis. This event was not life shortening since he ultimately died of widespread metastases. The final complication was a rapid demise in a patient who developed multiple organ infections, leukopenia, and anemia. In this instance, suppression of bone marrow by x-ray is suspected.

SUMMARY

1. An attempt has been made to evaluate the results of treatment of carcinoma of the esophagus by surgery and by super voltage x-ray.

2. Two patients with lower esophageal carcinomas had resection performed and lived 6 and 7 years.

3. The remaining 17 resected patients survived 0 to 34 months with an average of 8 months.

4. Mortality after resection was 36.8 per cent (7 patients).

5. Twenty-two patients treated by super voltage x-ray lived 1 to 28 months with an average survival of 9 months.

6. Significant palliation was achieved in 18 of the 22 patients.

7. Complications after x-ray therapy are for the most part related to the extent of the disease.

CONCLUSIONS

1. Carcinoma of the lower esophagus is primarily a surgical disease. X-ray therapy should be used only if surgery is specifically contraindicated, or possibly as an adjunct.

2. Carcinoma of the esophagus at all other levels is primarily an x-ray disease. The results of treatment achieved at the Hartford Hospital and elsewhere are at least as good as surgery, palliation is effective, and complications and mortality are minimal in a group of cases less favorable for treatment than the surgical group.

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THORACIC DUCT LIGATION

Its Effect on Lymphatic Spread of Gastrointestinal Tumors in Rabbit

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(From the Roswell Park Memorial Institute)

IN THIS study, the effect of ligation of the thoracic duct on the lymphatic spread of the malignant tumors of the gastrointestinal system has been experimentally investigated.

MATERIAL AND METHOD

Albino rabbits were used as the experimental animal because their thoracic duct is large enough to ligate and transplantable tumor is available. A technique of effective ligation of the thoracic duct was developed using multiple ligatures covering 4 to 5 cm. of its course in the right chest, thus preventing establishment of lymphatic bypass around the ligated portion. The physiologic effects of the ligation on the lymph circulation were determined and the spread of tumor in ligated and nonligated animals was studied.

Anatomy of the Thoracic Duct.—The thoracic duct originates from the cisterna chyli. It ascends along the aorta in the right retropleural space and changes its course to the left thorax at the level of the third or fourth intercostal space. In the thorax it appears as a single channel without tributaries. Two animals with loops along the course of the duct in the lower thorax were excluded from this study because of a possible bypass of the ligated area. The average diameter of the duct, 1 to 2 mm., varies with the animal's weight and physiologic status and the amount of fluid injected intraperitoneally.

Contrary to a report by Bunting and Huston,[1] we did not find that the rabbit has independent right and left thoracic ducts. Staining of the lymphatics with Evans blue dye and ligation of the right thoracic duct failed to reveal a left channel. In every animal the diaphragmatic lymphatics were stained much darker than the thoracic duct. These lymphatics are large channels forming a plexus under the diaphragmatic pleura. The larger collecting channels join the parasternal lymphatic trunks anteriorly and the thoracic duct posteriorly.

Oden, Bellman, and Fries[2] found that in mice, after intraperitoneal injection of Thorotrast, the parasternal lymphatics and the lymph nodes at the thoracic inlet could be visualized radiologically. Their findings in mice are analogous to our findings in rabbits. In brief, the thoracic duct drains the lymphatics of the parietal peritoneum, the visceral peritoneum, and most of the intra-abdominal viscera. The parasternal trunks, one on each side of the midline along the internal mammary vessels, drain both the peritoneal and pleural surface of the diaphragm.

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Technique of Ligation.—The thoracic duct of rabbits is a tiny nonvisible structure. However, since it drains the peritoneal lymphatics, it can be easily identified with the aid of Evans blue dye injected into the peritoneal cavity. For this purpose 3 c.c. of 1 per cent Evans blue dye was injected intraperitoneally into the rabbit under Nembutal anesthesia. The right thorax and the anterior part of the neck were then shaved and prepared for surgery.

About 2 hours later, with the rabbit still under Nembutal anesthesia, the trachea was exposed through a midline incision in the neck, opened longitudinally through 4 or 5 cartilaginous rings, and cannulated with a 2H Magill catheter for endotracheal oxygenation.

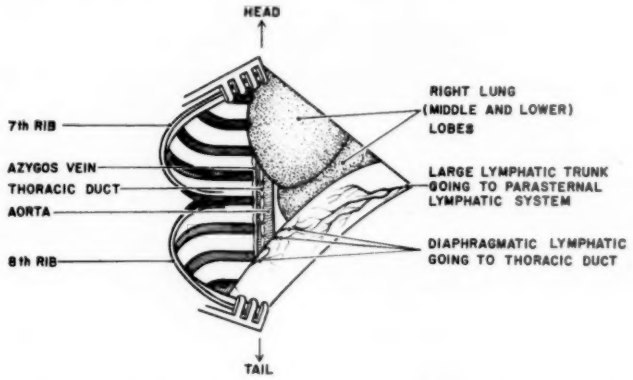


Fig. 1.—The posterior part of the diaphragmatic lymphatic plexus drains into the thoracic duct, the anterior part goes to the parasternal lymphatic trunks. After the ligation, the anastomosis between these two parts enlarged and the parasternal system took over the lymph circulation.

With the animal in a right lateral position, a right thoracotomy incision was made and the pleural cavity was entered through the seventh intercostal space. The lung was retracted anteriorly. The stained thoracic duct could be easily identified in the retropleural space as a threadlike structure lying in the right paravertebral gutter, beween the azygous vein and the aorta. Diameter of the duct varied from 1 to 2 mm. in the lower portion of the thorax, and tapered toward the head. The pleura along the medial side of the thoracic duct was incised, and 4 to 5 cm. of the duct was exposed and dissected away from the aorta. Four or five ligatures of 6-0 silk, 5 to 6 mm. apart, were then applied. The first ligature was applied at the most cephalad position because subsequent dilatation of the lower portion of the duct made lower ligatures more easily applicable. The ligated portion of the duct was then obliterated by injecting a sclerosing agent, 5 per cent sodium morrhuate, in and all around it. The chest cavity was closed in layers, the endotracheal tube removed, and the trachea closed by interrupted fine silk sutures (Fig. 1).

Physiologic Effects of Ligation.—Following thoracic duct ligation, the rabbits failed to eat for 2 days but continued to drink water. They passed soft stools for 4 to 5 days and lost considerable weight for 7 to 9 days, after which their appetite improved and weight was regained.

All rabbits underwent celiotomy 3 to 6 days after ligation for examination of the peritoneal cavity and/or implantation of V2 carcinoma in the

bowel wall. At this time, 50 to 100 c.c. of either chylous ascites or serous transudate was found in 60 per cent of the rabbits. These rabbits were more susceptible to infection and, if infected at the celiotomy, usually died with peritonitis. All rabbits showed edema of the mesenteric root lymph node (pancreas of Aselli) (Fig. 2) and the retroperitoneal tissues. When the animals were sacrificed 2 to 4 weeks after ligation, lymph stasis had usually disappeared completely. This may have been the result of collateral lymph circulation developing between the subdiaphragmatic part of the thoracic duct and

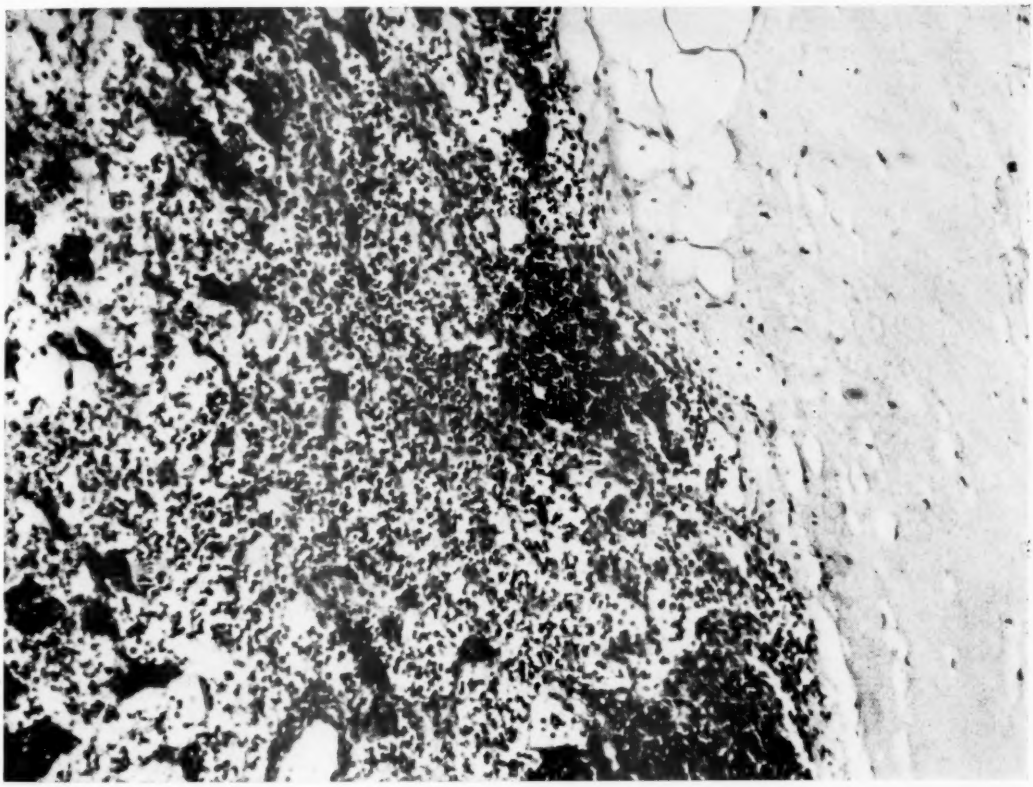
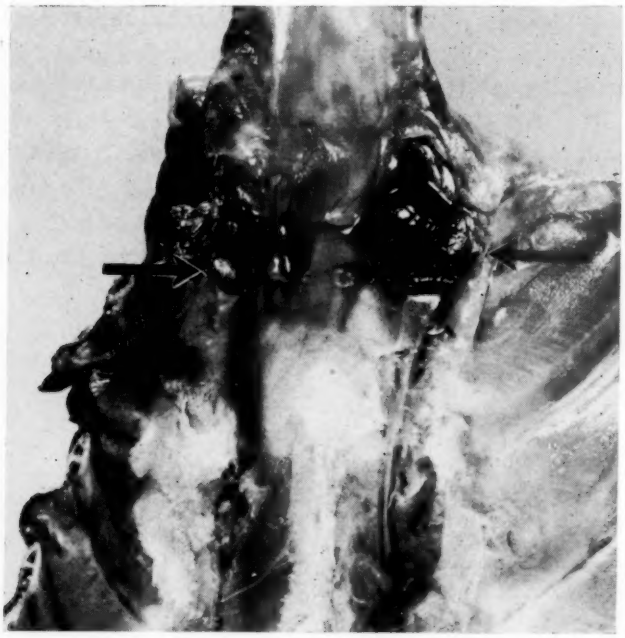


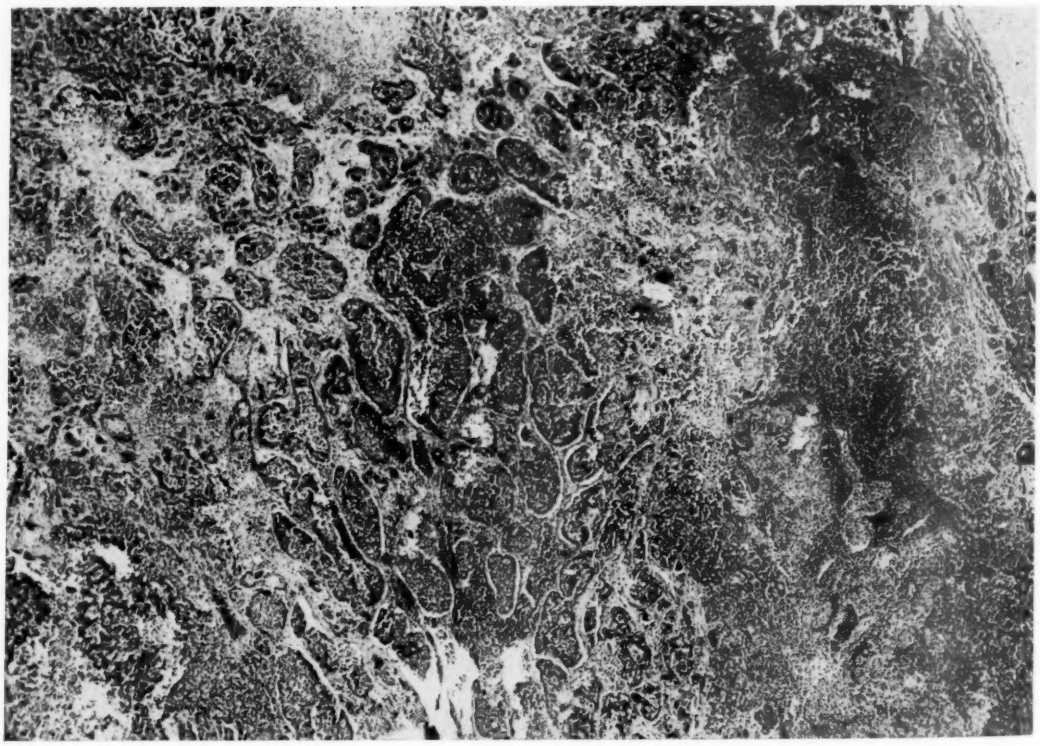
Fig. 2.—Mesenteric lymph node of a rabbit, sacrificed 24 hours after ligation of the thoracic duct, shows lymph stasis microscopically.

the parasternal lymphatic system through the diaphragmatic lymphatics. Collateral lymphatics were observed in 2 rabbits 3 months after thoracic duct ligation, when a second injection of Evans blue dye showed complete obstruction of the thoracic duct and staining of the diaphragmatic lymphatics and parasternal lymphatic trunks. Therefore, after duct ligation, lymph from the gastrointestinal system, instead of draining through the thoracic duct, must take a new route through the diaphragmatic and lower anterior chest lymphatics to the larger parasternal lymphatic channels.

Spread of V2 Carcinoma in Ligated and Nonligated Rabbits.—Thirty-five rabbits received injections of a cell suspension of the transplantable V2 rabbit carcinoma. With a 27-gauge needle, 0.3 to 0.5 c.c. of the suspension, containing 5 to 10 million single cells per cubic centimeter plus small clumps,



A.



B.

Fig. 3.—*A*, The inner aspect of the upper sternal bone area. *Arrows* show the affected parasternal lymph nodes. B, The microscopic appearance of one of the affected parasternal lymph nodes.

was injected subserosally into the transverse colon wall. To determine the pathway of immediate dissemination of fluid injected at the subserosa, two other rabbits received Evans blue solution instead of the tumor cell suspension. Within a few seconds, the lymphatics of the mesentery were stained to the root, suggesting that the tumor cells disseminate primarily by way of the lymphatics at the site of injection.

Twenty of the 35 rabbits had their thoracic ducts ligated within a week prior to tumor cell inoculation; the remaining 15 rabbits were nonligated controls inoculated with tumor cells. To duplicate a possible effect of Evans blue dye on tumor metastases, the nonligated animals had been injected with the dye a few days prior to tumor cell inoculation. Nine of the ligated and 7 of the nonligated animals died of intestinal perforation due to the tumor growth and are not included in this study. All surviving rabbits were sacrificed and autopsied 5 weeks after tumor cell inoculation; metastases were noted.

Fig. 4.—The cut surface of the involved parasternal lymph node. The large necrotic area is characteristic of V2 carcinoma.

RESULTS

Sites of metastases in the individual ligated and nonligated animals sacrificed 5 weeks after tumor cell inoculation are listed in Table I. The major difference between the two groups was the finding of lymph node metastases in the superior parasternal region of the ligated animals only. In 9 of the 11 ligated animals, these nodes were 10 to 15 mm. in length, grossly, and in most cases were bilaterally involved with tumor (Fig. 3, *A* and *B*) and showed the central necrosis characteristic of V2 carcinoma (Fig. 4). Of the 8 nonligated animals, only 1 showed parasternal lymph node involvement; furthermore, in this animal massive infiltration of the entire group of intrathoracic lymph nodes and the lungs was observed.

Gross lung metastases were found in 6 animals of each group, and were accompanied by liver metastases in 4 ligated and 5 nonligated animals (Fig.

TABLE I

RABBIT NUMBER	BOWEL WALL	MESENTERY NODE	LIVER	LUNG	PARASTERNAL NODE
		Nonligated Animals			
1	+	+	+	△	–
2	+	+	+	+	+*
3	+	+	–	–	–
4	+	+	+	+	–
5	+	+	+	+	–
6	+	+	+	+	–
7	+	+	+	–	–
8	+	+	–	+	–
		Ligated Animals			
9	+	+	–	+	+
10	+	+	+	△	+
11	+	+	–	–	+
12	+	+	+	+	+
13	+	–	+	+	+
14	+	+	+	△	+
15	+	+	+	+	–
16	+	+	–	–	+
17	+	+	+	–	–
18	+	+	–	+	+
19	+	+	–	–	+

+ Denotes the site of gross metastases; △ microscopic lung metastases; – denotes no gross metastases.

*Infiltration of entire groups of intrathoracic nodes.

Fig. 5.—The mesenteric lymph node, the liver, and the lung metastases.

5). Whenever gross metastases were detected in the liver, invariably there were also metastases to the lungs, gross metastases in most animals and microscopic in the others (Fig. 6).

Gross liver metastases were found in 6 animals of each group.

The large lymph node at the root of mesentery (pancreas of Aselli) was grossly involved by metastases in all animals of both groups.

Metastatic involvement of muscles of the lower chest wall, the upper abdominal wall, and the diaphragm was more frequent in the ligated animals. The spread of tumor in the abdominal lymph nodes had no characteristic pattern in both groups. However, while gross metastases involved the bowel wall and mesenteric lymph nodes in both groups, they were more localized in the nonligated animals, indicating that dissemination of the tumor in the gastrointestinal system is more extensive in the ligated animals.

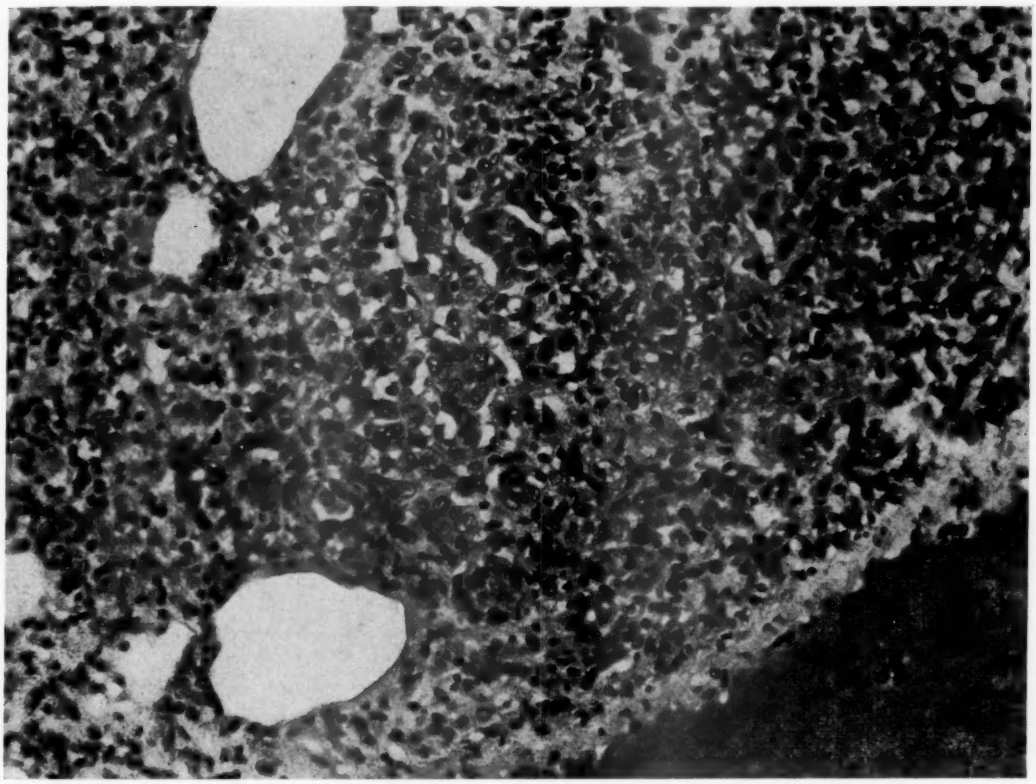


Fig. 6.—The microscopic foci of metastases in the lung.

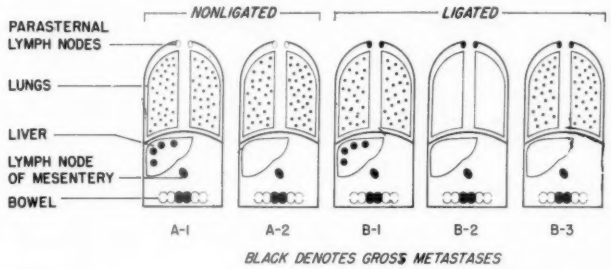


Fig. 7.—The types of distribution of metastases in nonligated and ligated rabbits.

DISCUSSION

The different types of distribution of metastases in the nonligated and ligated animals is illustrated in Fig. 7. The types *A-1* and *A-2* represent sites of metastases in nonligated animals; in this group of animals the parasternal

lymph nodes were not involved. The types *B-1, B-2,* and *B-3* represent different types of distribution in ligated animals; characteristic of this group was metastatic involvement of the parasternal lymph nodes.

All animals of both groups had metastases in the mesenteric lymph node. This is a result of the technique of tumor cells inoculation. As was mentioned earlier, injection of the cell suspension into the bowel wall subserosally results in immediate lymphatic spread.

Several of these animals in each group also had liver metastases in addition to the metastases in the mesenteric lymph node (types *A-1* and *B-1*). These hepatic metastases probably represent the blood vessel spread of tumor cells, which is not as immediate as the lymphatic spread. It may not occur until after tumor growth is established at the primary inoculation site.

Contrary to the cortisone-treated animals,[3] no arterial dissemination was evident in any of our experiments. No animals had eye, adrenal gland, kidney, spleen, ovary, or testicle metastases.

The absence of the liver metastases may indicate the pure lymph-borne origin of the lung metastases in types *A-2* and *B-3*. The lung metastases in type *B-3* is associated with the parasternal node metastases, while in type *A-2* there is no such combination. This difference is due to the ligation of the thoracic duct. The lung metastases in type *A-2* represent the pure thoracic duct spread, and in type *B-3* they represent the pure parasternal lymphatic spread. The parasternal node metastases in type *B-2* and parasternal node and lung metastases in type *B-3* represent two different phases of the pure parasternal lymphatic spread. Probably, the lung metastases in type *B-3* indicate the more advanced phase. The lung metastases in types *A-1* and *B-1* might be due to both kinds of spread. Probably, in these cases the blood vessel spread followed the lymphatic spread.

CONCLUSIONS

1. When the lower part of the thoracic duct of the rabbit is ligated, collateral lymphatic circulation is established between the thoracic duct system and the parasternal lymphatic system.

2. When V2 carcinoma is inoculated into the wall of the gastrointestinal system of the rabbit, the spread of tumor cells by the lymphatics is as important as that by the blood vessels.

3. Ligation of the lower part of the thoracic duct does not prevent the lymphatic spread of tumor cells to the lungs. In addition, tumor metastases develop in the parasternal lymph nodes, in the muscles of the lower chest and upper abdominal wall, and in the diaphragm because of the newly established collateral lymphatic circulation.

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ENERGY EXPENDITURE OF SURGEONS, NURSES, AND ANESTHESIOLOGISTS DURING OPERATIVE PROCEDURES

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THE energy expenditure of people engaged in different trades and occupations has been recorded.[8, 9] Also, the expenditure of patients undergoing physical therapy has been investigated.[4] In the present study the energy output of surgeons, nurses, and anesthesiologists was determined during operative procedures. The results were used to calculate the work cost of these activities.

METHODS

Indirect calorimetry was used to determine the energy output of 11 doctors, 4 nurses, and 1 attendant during 22 surgical procedures. Collection and measurement of the volume of expired air was simplified by the use of a light, portable respirometer which measured the volume of the expired air and simultaneously diverted 0.3 or 0.6 per cent into a small rubber bladder.[7] The use of this machine in carrying out indirect calorimetry in man has been described by Insull.[6] A face mask† was strapped on the subject and connected to the meter which was either fastened on his back or hung from a conveniently placed stand. The air line which connected the mask to the meter was passed either over his shoulder or his head. This allowed an unobstructed view of the operative area. Precautions were taken so that the operating field was not contaminated by any of the equipment. Measurements were made for periods of 15 to 45 minutes, during which the subject performed various tasks. Four individuals had several tests carried out over a period of days, during which different procedures were performed. In the case of the nurses and anesthesiologists the period of study covered the time in which they were carrying out all of the tasks involved in performing a specific duty (e.g., the test period for an anesthesiologist who was giving a spinal included the work involved in walking back and forth to the anesthesia cart to obtain equipment and drugs in addition to the actual administration of the anesthetic agent).

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†A modified anesthesia mask was used in the initial work; later the Air Force oxygen demand mask #MS 22001 was employed.

The oxygen content of the expired air was determined in a Beckman Oxygen Analyser. Energy expenditure was calculated from the volume and the oxygen content of the expired air by application of the Weir formula[10]:

$$\text{cal./min.} = \frac{1.0548 - 0.0504\ O_e \times L}{1 + 0.082P}$$

where O_e is the oxygen content of the expired air, P, the decimal fraction of the total caloric intake derived from protein, and L, the pulmonary ventilation per minute corrected for temperature and pressure and reduced to dryness. These calculations were simplified by the use of a table of values derived from the Weir formula and dependent upon the oxygen content of the expired air and the protein content of the diet.[3] It was assumed that the subjects received 10 per cent of their total caloric intake from protein.

The total error of the procedure, exclusive of variation inherent in the use of the Weir calculation, was estimated by Insull[6] by considering the individual errors contributed by the various components of the system. He found that some of the errors were routinely positive and others negative. The range of maximum error was estimated by summation of all the errors first when they were exerting their maximum positive affect (+1.48 per cent) and then when they were exerting their maximum negative affect (-13.88 per cent). The reproducibility of the determination was checked by performing four successive studies on one individual who remained at bed rest. An average energy expenditure of 0.875 cal. per minute was found with a standard deviation of 0.12 cal. per minute.

RESULTS

The energy expenditure of surgeons, nurses, and anesthesiologists during various procedures is presented in Table I. The number of individuals studied and the range of values found for different operations and activities are listed in Table I.

Procedures which require more muscular activity usually have a greater energy cost. Preoperative scrubbing of the surgeons' hands, a vigorous procedure, required an average of 2.6 cal. per minute, whereas the energy expenditure required for a herniorrhaphy was only 1.8 to 1.9 cal. per minute. The repair of a sacral decubitus ulcer, which is a more extensive surgical procedure, required a similar expenditure of energy (1.9 to 2.1 cal. per minute). However, performing an amputation required considerably more physical effort and showed a much greater energy expenditure (2.8 to 3.2 cal. per minute).

Three anesthesiologists were studied. Their energy output during administration of anesthesia was 1.8 to 2.6 cal. per minute. This expenditure was greater than that noted for some operative procedures. The energy output of the scrub nurses (1.5 to 2.1 Cal. per minute) was found to be approximately that of the operating surgeon when he was carrying out procedures that require moderative physical activity. As expected, the circulating nurse who was moving about supplying needed material to the surgical team demonstrated a much larger energy output (2.7 cal. per minute). The largest energy

output recorded in this study was that of an orderly who used an electric cast cutter to remove a body cast. This procedure required the use of a rapidly vibrating tool and considerable struggling with the cast.

TABLE I. ENERGY EXPENDITURE OF OPERATING ROOM PERSONNEL

PERSONNEL AND PROCEDURE	NUMBER OF TESTS	RANGE OR SINGLE VALUES (CALORIES PER MINUTE)
Surgeon		
Preoperative hand scrub	3	2.3-2.8
Biopsy of lymph nodes or muscle	3	1.7-2.6
Inguinal herniorrhaphy	2	1.8-1.9
Diaphragmatic herniorrhaphy	1	2.7
Closure of sacral decubitus ulcer	2	1.9-2.1
Suprapubic prostatectomy	1	2.1
Removal of nails and plate from hip	3	2.3-3.0
Amputation of leg	2	2.8-3.2
Closure of abdomen	2	2.1-2.3
Assistant surgeon		
Prepare operative field	1	2.2
Retract muscles	3	1.5-1.6
Nurse		
Scrub nurse	3	1.5-2.1
Circulating nurse	1	2.7
Anesthesiologist		
Local	1	2.6
Spinal	1	2.5
General	1	1.8
Orderly		
Remove body cast	1	3.5

TABLE II. RANGE OF ENERGY EXPENDITURE FOR INDIVIDUAL SURGEONS DURING VARIOUS OPERATIVE PROCEDURES

SURGEON	PROCEDURE	ENERGY EXPENDITURE (CALORIES PER MINUTE)
W. D.	Assistant, retract muscles	1.5
	Biopsy of lymph nodes	1.8
	Inguinal herniorrhaphy	1.9
	Closure of sacral decubitus ulcer	1.9
	Diaphragmatic herniorrhaphy	2.7
	Preoperative hand scrub	2.8
	Bed rest and fasting	1.3
C. H.	Assistant, retract muscles	1.6
	Closure of sacral decubitus ulcer	2.1
	Preoperative hand scrub	2.7
	Bed rest	1.1

The range of energy expenditure for two surgeons during various procedures is presented in Table II. Surgeon W. D. was studied during 6 operative procedures and at bed rest. His energy output while holding retractors was only a little greater than that measured at bed rest (1.5 versus 1.3 cal. per minute). It was interesting that the largest energy output obtained in his case occurred when he was scrubbing his hands in preparation for surgery. Surgeon C. H. also expended more energy while scrubbing his hands before surgery than he did during the subsequent operation, the repair of a sacral

decubitus ulcer, or while holding retractors. C. H. expended 2.7 cal. per minute while scrubbing, 2.1 cal. per minute while operating, and only 1.6 cal. per minute while holding retractors.

DISCUSSION

Those interested in the physiology of work have arbitrarily divided muscular activity into four different categories depending upon the caloric expenditure.[2] Light work includes expenditure up to 1.25 cal. per minute. Moderate work requires an energy output of 1.25 to 2.5 cal. per minute and hard work from 2.5 to 5.0 cal. per minute. For very hard work the energy expenditure is above this value. According to this classification most of the surgical procedures studied may be regarded as light or moderate work. Amputations and certain orthopedic operations which involve increased muscular activity should be considered hard work (energy expenditure greater than 2.5 cal. per minute).

Some common activities which have energy expenditures less than 2.5 cal. per minute are sitting, playing cards, and playing many musical instruments, possibly with the exception of the organ and drums.[9] The energy expended by a member of a surgical team is similar to values found for certain trades and occupations such as armature winding, radio repairing, printing, bookbinding, tailoring, repairing shoes, or repairing locks. Most recreational activities usually have greater energy expenditures; for instance, golf, 5, horseback riding, 3 to 10, and dancing, 5 to 7 cal. per minute.

A true comparison of the total energy expenditure for various activities cannot be made without reference to the total time required to perform each activity. Although the energy expenditure per minute was greater when W. D. and C. H. were scrubbing their hands preoperatively than during the subsequent operation, this activity was of relatively short duration (5 minutes). The total energy output should be calculated from the product of energy cost per minute and the duration of the activity. The average time required for the repair of a large sacral decubitus ulcer is 2 to 3 hours. The total energy expenditure for this procedure therefore more properly should be considered as 240 to 360 calories, while the total energy expenditure for preoperative hand scrubbing is only 14 calories.

The increased mental activity of the surgeon during an operation is an energy-consuming process. It is known that the brain has a high rate of oxygen utilization. However, Benedict and Benedict[1] have shown that mental effort contributes an insignificant addition to the total energy expenditure of the body. In fact, the effect of mental effort is so small that the most accurate apparatus and very carefully controlled conditions are necessary to detect any increased energy expenditure.

It may be concluded from this study that the work load for members of the surgical team is not greater than that which is found in many sedentary activities. However, the measurement of energy expenditure (oxygen consumption) relates to whole body activity and is only one of the parameters of physiologic strain. Anxiety and nervous tension may cause surgery to be fatiguing

and thus "hard" work in spite of its "light" nature by energy standards. The role of anxiety and nervous tension in the energy expenditure of the surgeon has not been evaluated in this study. If tension contributed to the total energy expenditure, it was measured; however, it was not possible to fractionate it from the total expenditure measured. Since only cooperative subjects were studied, it is possible they did not suffer excessive amounts of anxiety during the operative procedures. Hellerstein and associates[5] have work in progress which may help to evaluate the role of anxiety and the work of various organs in the total energy expenditure of surgeons.

CONCLUSIONS

Using methods of indirect calorimetry, the energy production of the operating team, that is, surgeons, assistants, nurses, and anesthesiologists, was determined. The energy expenditure for most tasks fell in the range considered to be light and moderate work, requiring less than 2.5 cal. per minute. However, the energy expenditure for circulating nurses and for surgeons when carrying out various orthopedic procedures fell into the class of hard work, requiring more than 2.5 cal. per minute.

We wish to express our appreciation to Dr. Charles A. Hubay and the nursing staff of Highland View Cuyahoga County Hospital for their cooperation in this study.

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PRIMARY CARCINOMA OF THE CARINA AND BIFURCATION SUCCESSFULLY TREATED BY RESECTION AND RECONSTRUCTION

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PRIMARY or secondary neoplastic disease involving the trachea is usually inoperable because of its extensiveness. Primary carcinoma of the carina is still a rarer occurrence. A few successful resections and reconstructions of carinal carcinoma have been reported by Juvenelle,[6] Barclay, and Björk[1] An additional case of a primary carcinoma is reported.

CASE REPORT

A 68-year-old white man was admitted to the University of Kansas Medical Center on Oct. 6, 1958. Initial symptoms consisted of a sore throat and anterior chest pain, without fever, beginning in April, 1958. Symptomatic antibiotic treatment relieved symptoms. Two weeks prior to admission a productive blood-streaked sputum was noted which was accompanied by vocal hoarseness and recurrent chest pain. Smoking history stated cigarette usage of one package daily for 30 years.

Physical Findings.—The blood pressure was 160/80 mm. Hg. No cardiac murmurs were present. Chest was clear to percussion and auscultation. Fingers and toes showed marked clubbing. No cervical or supraclavicular lymphadenopathy was present. The remainder of physical examination was within normal limits.

Laboratory and X-ray Findings.—Urinalysis and complete blood count were normal. VDRL was nonreactive. Blood urea nitrogen, fasting blood sugar, total and fractional proteins, and other hepatic function tests were normal. Tuberculin skin test was positive. Histoplasmin skin test was negative. Sputum was negative on smear for acid-fast bacilli. Cytologic study of the sputum showed many malignant cells. The electrocardiogram was normal. Chest x-rays showed heavy bilateral hilar shadows (Fig. 1). Hilar planograms were noncontributory. Bronchograms suggested a narrowing of the left main-stem bronchus, but otherwise were normal (Fig. 2). Bronchoscopy on Oct. 7, 1958, showed a friable, fungating tumor arising from the posterior carinal wall and extending bilaterally into each of the main-stem bronchi. Microscopic examination of the biopsied tumor mass showed a poorly differentiated squamous cell carcinoma. The patient desired to return home temporarily and returned for surgery on Oct. 21, 1958.

Operation.—General anesthesia consisted of endotracheal cyclopropane and oxygen. A right thoracotomy was done through the bed of the fifth rib. Exploration revealed normal hilar lymphadenopathy, with no palpable masses within the lung. The azygous vein was ligated and divided. The superior vena cava was mobilized and retracted medially. The trachea was exposed and all paratracheal lymph nodes were removed. The esophagus was not adherent to the carinal tumor. The segmental arterial blood supply to the distal trachea was identified and only one artery to the carinal area was ligated. The right and left main-stem bronchi were mobilized. The carinal tumor was dissected free

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of the aorta and pulmonary artery (Fig. 3). A linear incision was made in the left main-stem bronchus, 2 cm. below the tumor mass. A sterilized endotracheal tube was inserted through the incision in the left bronchus, the cuff was inflated, and the endo-

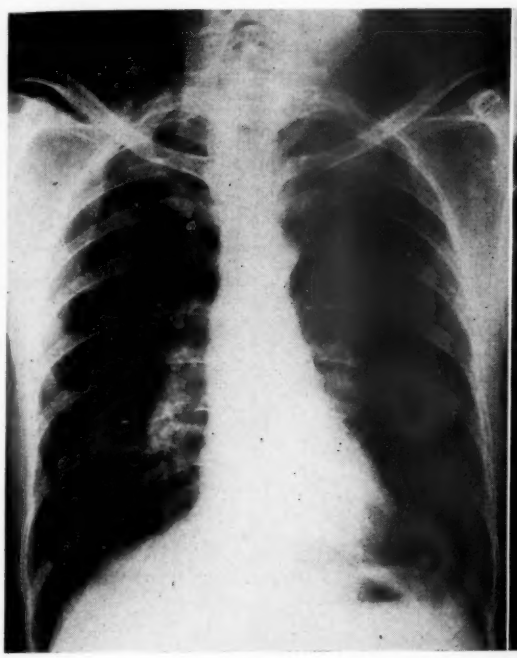

Fig. 1.

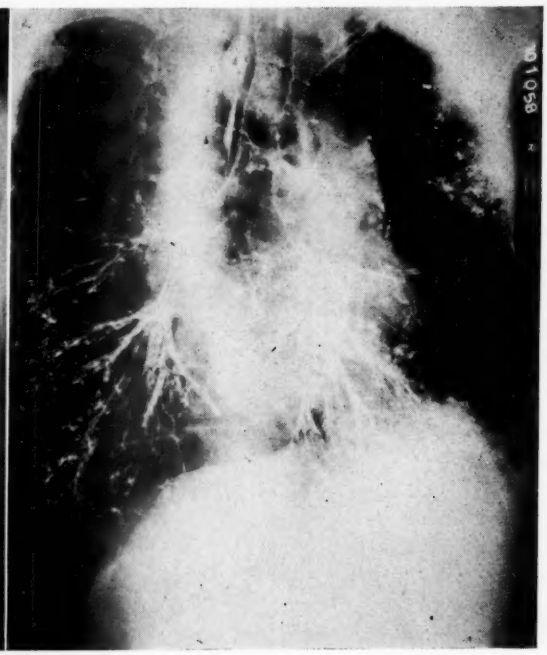

Fig. 2.

Fig. 1.—Preoperative chest x-ray showing bilateral hilar shadows.
Fig. 2.—Preoperative bronchograms outlining narrowing of the left main-stem bronchus.

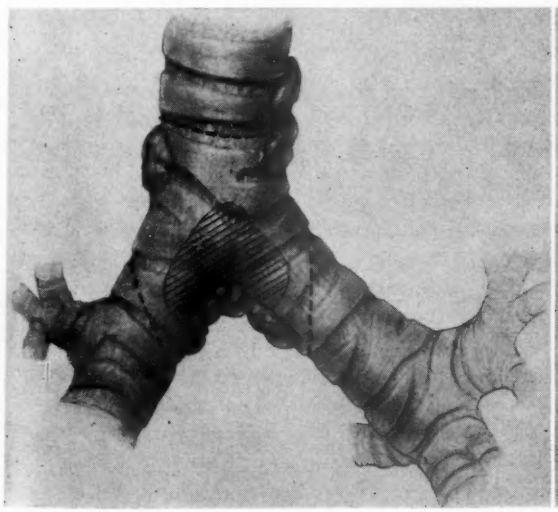

Fig. 3.

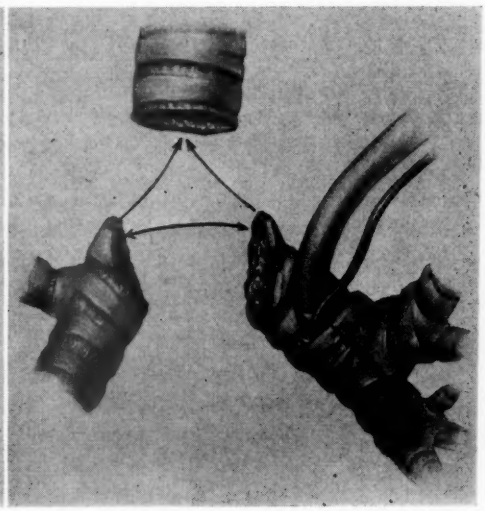

Fig. 4.

Fig. 3.—Extent of tumor involvement of the carina.
Fig. 4.—Method of aeration of left lung with a left endobronchial tube allowing en bloc resection of the trachea and carina.

bronchial tube was connected to the anesthesia machine. The left lung was then utilized for aeration (Fig. 4). An en bloc resection of the distal trachea, carina, and main-stem bronchi was done. The bronchi were resected obliquely in order to facilitate reconstruction

of a new carinal angle. The line of tumor excision extended two cartilaginous rings proximal and distal to the tumor. The obliquely severed ends of the bronchi were sutured together posteriorly and superiorly. Superiorly, the then presenting circumference of the anastomosed bronchi was sutured to the trachea. An anterolateral diamond-shaped defect, 1.5 cm. at the widest diameter, was filled with a patterned free autogenous cartilage graft and fixed with interrupted sutures (Fig. 5). This autologous cartilage graft was obtained from the lateral uninvolved portion of the right main-stem bronchus. Tracheal and bronchial anastomosis was done with 3-0 and 4-0 black silk. The left endobronchial tube was removed; the linear incision was closed with interrupted 4-0 black silk sutures. The remainder of the procedure was done with anesthesia given through the endotracheal tube. Layered adjacent pleural and mediastinal areolar tissue was sutured over the reconstructed carina to provide an air seal. The right lung was expanded and no air leakage was seen. Anterior and posterior drainage tubes were inserted. The chest wall was closed in layers. A 500 c.c. blood loss was replaced and the patient returned to the recovery room in good condition.

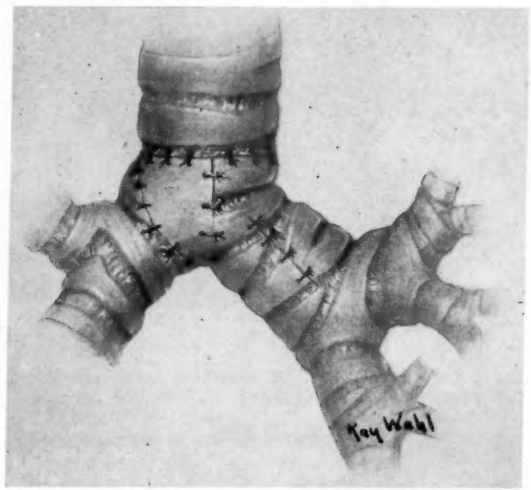

Fig. 5.—Reconstructed carina completed with the aid of a free autogenous cartilage graft.

Postoperative Course.—The postoperative course was uneventful. Prophylactic doses of penicillin and streptomycin were given for 7 days. Oral saturated solution of potassium iodide was given to thin bronchial secretions. Postoperative x-rays showed good expansion of both lungs. Pathologic examination of the surgical specimen reported a poorly differentiated squamous cell carcinoma of the carina. Three of the six removed peribronchial nodes and five of the nine tracheal nodes contained tumor.

The patient was readmitted for the third time on Dec. 4, 1958. He was free from cough, dyspnea, or hemoptysis. His only complaint was mild incisional pain.

Postoperative bronchoscopy visualized a well-healed anastomosis (Fig. 6). The free cartilage graft was viable and the suture lines were healed. The main-stem bronchi showed no stenosis. Postoperative bronchograms also outlined the reconstructed carina without stenosis.

DISCUSSION

Resection of the trachea for primary or secondary malignancy, when extensive involvement is present, remains an unsolved problem. Experimental methods of reconstruction have consisted of excision and anastomosis of the proximal and distal segments,[4] replacement of the surgical defect by autogenous[1] or homologous grafts,[5] metallic, glass, or plastic protheses,[3] and

metallic mesh supported by free grafts.[7] The failure of these replacement or reconstructive methods are due to avascular necrosis, absorption of cartilage, late stenosis, leakage, and retained secretions, due to the loss of normal ciliary action. An experimental direct anastomosis of the right main bronchus to the trachea followed by an end-to-end anastomosis of the left main bronchus seems promising.[1]

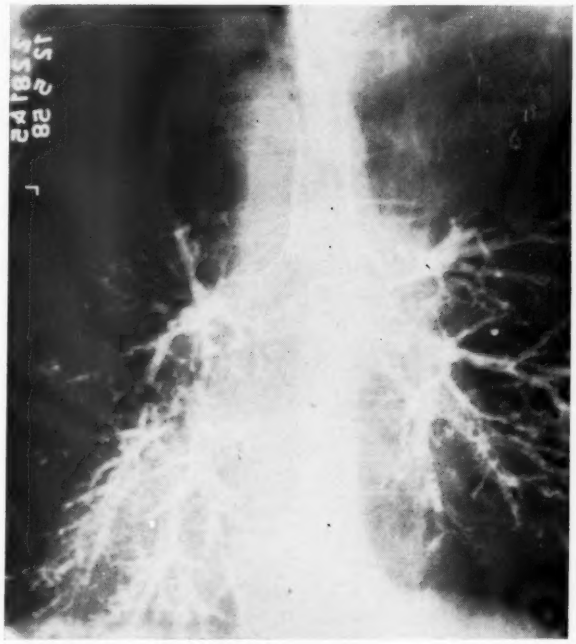

Fig. 6.—Postoperative bronchograms showing a well-healed anastomosis without stenosis.

In order to accomplish resection and reconstruction of the trachea or carina successfully, one should strive to attain the criteria set forth by Carter and Strieder.[2] The conditions to be met are the maintenance of an adequate airway, an airtight anastomosis, a mucus-free postoperative period, no late stenosis, and minimal bacterial contamination at the time of surgery. We feel that other factors, including minimal tracheal mobilization and consequent preservation of segmental blood supply, are of importance. The absence of tension on the suture line prevents a strangulating necrosis. In this case, the use of an autologous cartilage graft accomplished adequate anastomosis without tension. The main-stem bronchi received their blood supply via the pulmonary circuit.

SUMMARY

A case of successful resection of primary bronchogenic carcinoma involving the carina and bifurcation has been reported. Reconstruction with preservation of both main-stem bronchi was aided by means of a free cartilage graft. A brief review of methods and criteria to accomplish this procedure are presented.

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RENAL ECTOPIA

Report of a Case of Fused Pelvic Renal Ectopia

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INTRODUCTION

ECTOPIA is not a particularly rare renal anomaly. It was discovered 30 times among 17,229 intravenous pyelographic examinations performed at the Mallinckrodt Institute of Radiology between 1950 and 1959. The types of renal ectopia represented among these 30 cases were: unilateral ectopia (20 cases), crossed ectopia (8 cases), unilateral renal agenesis with pelvic ectopia of the one kidney (1 case), and fused pelvic ectopia (1 case). The above types of renal ectopia are illustrated diagrammatically in Fig. 1.

The extreme rarity of fused pelvic kidneys (cake kidney, disc kidney, shield kidney, or lump kidney) constitutes the reason for this case report.

Historically, Cruveilhier (1884)[3] described "two kidneys fused both occupying the rear of the rectum." Botez (1912)[2] and Gruber (1927)[7] each found 4 cases of fused pelvic renal ectopia, and recently Burckhart[4] added a case found in a woman who had undergone a normal pregnancy and delivery. At least 10 cases[6, 8, 10-13] have been reported in English. Campbell[5] discovered 4 cases among 50,000 necropsies (1:12,500).

The majority of fused pelvic kidneys that have been discovered were unsuspectedly found during necropsy. A few have been found during a celiotomy performed in order to ascertain the cause of hematuria. Campbell reported a single case of a silent abdominal tumor that was demonstrated to be a fused pelvic kidney by pyelography. At least 4 have been reported in which an anuric death followed the removal of a pelvic tumor that was later found to be constituted of fused pelvic kidneys—the only renal tissue the persons had.[4] Consequently, the possibility of the existence of renal ectopia must always be borne in mind and that possibility ruled out by pyelography before removing palpable retroperitoneal abdominal tumors, especially when they are located within the lower abdomen and pelvis—abnormal sites for kidneys. A case of fused pelvic kidney that we report demonstrates this point.

CASE REPORT

An unskilled laborer, 24 years old, sought to have an easily reducible indirect inguinal hernia repaired. He had no genitourinary complaints and had not been conscious of anything being wrong within his abdomen. He was a healthy, strong Negro. He had a blood pressure of 140/90 mm. Hg. A slightly tender mass that was difficult to feel existed in the right lower abdominal quadrant; it seemed to extend toward the left, crossing

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the midline. The mass could not be felt through the rectum. Radiographic examinations of the upper gastrointestinal tract and colon showed only displacement of the small bowel from the lower abdomen and pelvis. Thereupon, the possibility that this mass was constituted of renal tissue was entertained. Intravenous pyelography failed to demonstrate kidneys in their proper positions. Subsequently, a cystoscopic examination was performed. The vesical interior was normal as were the locations of both ureteral orifices. Ureteral catheters could only be passed a short distance before resistance to their passage was felt.

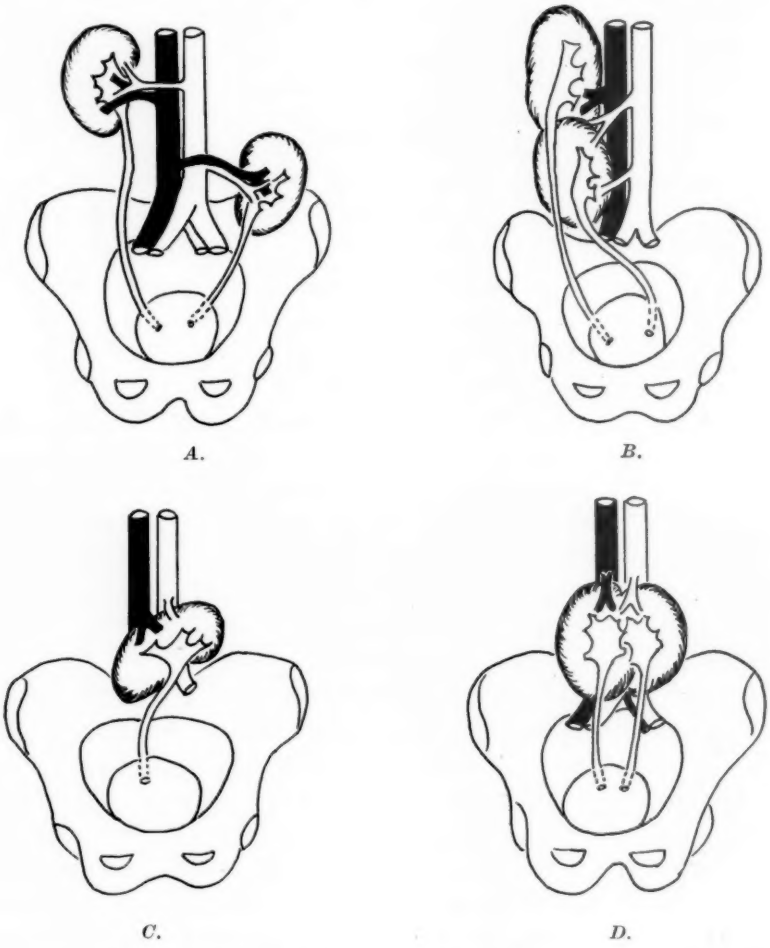

Fig. 1.—Types of renal ectopia found in 17,000 intravenous pyelographic examinations. *A*, Unilateral renal ectopia. *B*, Crossed renal ectopia. *C*, Single pelvic renal ectopia. *D*, Fused pelvic Renal Ectopia.

A roentgenogram of the lower abdomen taken before contrast medium was injected demonstrated fusion of the anomalous kidneys by virtue of the proximity of the catheters (Fig. 2). The postinjection film was unsatisfactory. Two days later, ureterograms were obtained using acorn-bulb catheters. These showed short ureters and fused pelvic kidneys with their pelves pointing inferiorly. The configurations of the collecting systems were normal (Fig. 3 and 4). Following this examination a right inguinal herniorraphy was performed *and the mass was not molested.*

What catastrophe may have befallen this man should the nature of this mass not have been determined pyelographically?

Fig. 2.—Flat plate showing ureteral catheters in place.

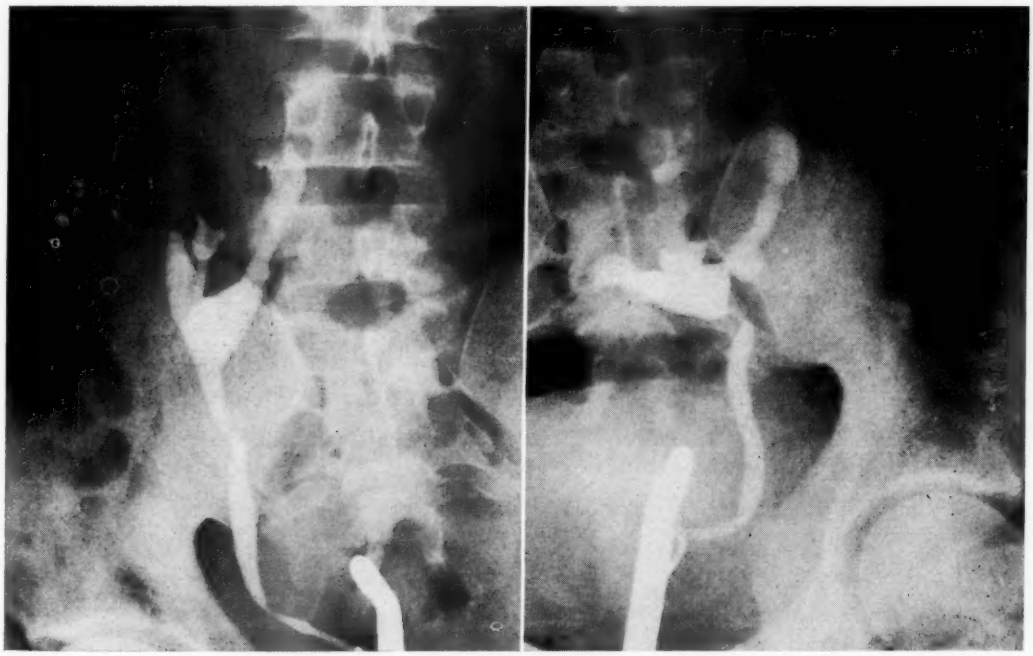

Fig. 3.

Fig. 4.

Fig. 3.—Right retrograde pyelogram of fused pelvic kidney.
Fig. 4.—Left retrograde pyelogram of fused pelvic kidney.

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OBSERVATIONS OF THE CARDIOVASCULAR SYSTEM IN EXPERIMENTAL TRAUMATIC SHOCK

I. General Hemodynamics

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IN RECENT years, an intensive exploration has been made in these laboratories of the response of animals to extensive mechanical injury. The animal preparation which has been used for these studies has been reported previously.[28] In brief, massive bilateral hind leg injury is established in Texas angora goats. In the absence of prompt and adequate débridement, the preparation proves uniformly lethal. However, the survival time after injury can be varied considerably by the use of certain appropriate antibiotics or by the transfusion of large amounts of whole blood.[23] The experiments have therefore dealt with a situation which presents the clinical features of blood loss and tissue injury, as well as superimposed infection. For this reason, it is believed that data derived under these conditions may have applicability to certain problems encountered in treatment of trauma, both on the battlefield and in civilian practice.

The nature of the infectious process which develops in the wound and which has a marked effect on the survival time of the goats after injury has received considerable attention. A quantitative analysis of the wound flora revealed that the antibiotics which proved effective in prolonging the survival of the animals acted by depressing the gram-positive organisms. Although a wide bacterial spectrum was noted, the organisms which shortened survival were those sensitive to penicillin and Aureomycin and not to streptomycin.[29] More recent studies have shown that, of these gram-positive organisms, the pathogenic clostridia appear to be most related to variation in survival.[22]

The studies which are herein recorded were undertaken to evaluate the cardiovascular response of the injured animals in the presence of these noxious stimuli. The use of effective anticlostridial antibiotics permitted variation of the stress and therefore of survival time.

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METHODS

Texas angora goats (castrated), weighing between 30 and 50 kilograms were used. The animals were prepared for physiologic study under pentobarbital sodium anesthesia (10 to 12 mg. per kilogram). The external jugular vein was catheterized with a polyethylene tube, the catheter was advanced to approximately the right atrium to collect common venous blood. Either the brachial or common carotid artery was cannulated with polyethylene tubing for collection of the arterial samples and the recording of arterial pressure. A soft rubber tracheostomy cannula was inserted. Approximately 2 hours elapsed before the initial observations were made in order to allow the variable features of anesthesia to dissipate.

The arterial pressure and pulse were measured with a Sanborn electromanometer connected with a Poly-Viso recorder. After these values were obtained, 2-ml. samples of blood were drawn from the venous catheter and from the arterial cannula and discarded. Then, with oiled, heparinized syringes, samples of arterial and venous blood were drawn simultaneously. Approximately 15 ml. of each was collected over an interval of from one to 2 minutes for pH determination and gas analysis. The tracheal cannula was then fitted to a Sanborn Metabolator and the respirations were observed for a period of approximately 10 minutes in order to calculate oxygen consumption and minute volume of respirations.

The blood samples were immediately warmed to 38° C. (normal goat body temperature) in a constant temperature bath and the pH was determined on a Beckman pH meter, the electrodes of which were also maintained at the same temperature. The samples were then promptly analyzed on a Van Slyke manometric apparatus for CO_2 and O_2 content. Oxygen capacity on both samples was determined after equilibration of the blood with room air for a period of one hour. From the foregoing data, the cardiac output was estimated by means of the direct Fick principle. The mean peripheral resistance was calculated by means of the formula.

$$\text{M.P.R} = \frac{\text{Mean Arterial Pressure (mm. Hg)}}{\text{Cardiac Output (ml./sec.)}}$$

The blood volume was estimated by the use of Cr^{51}-tagged erythrocytes. Distortion caused by concentration of red cells in the spleen was minimized by the use of intravenous epinephrine (0.5 mg.) given in conjunction with the injection of the tagged cells, as described by Anderson.[1] The hematocrit was obtained by the use of Wintrobe tubes, and the result was corrected for trapped plasma by multiplying by the factor 0.81 described by Klement[19] for this species of goat. Correction for body hematocrit/venous hematocrit factor was not made. In order to compensate for the variation in weight, those values which were influenced by the size of animals used were adjusted on a standard basis of quantity per square meter. The formula used for calculation of the surface area of goats was that used for sheep:

$$\text{S.A. } (M.^2) = 0.83 \times \text{Wt. } (kg.)^{2/3}$$

Following the initial control observation as described, the animals were then subjected to the standard bilateral hind leg injury. Under pentobarbital sodium anesthesia, small charges of tetryl, a high explosive, were detonated on carefully predetermined sites on the hind extremities. The major vessels bleeding at the wound site were clamped immediately after injury, and a clean but nonsterile dressing was loosely applied. The animals were then observed in a restrained prone position on a cart. The animal preparations show marked uniformity with respect to the size and resultant physiologic effects of the wound.

The observations of the above indices were made from three groups, each of 8 animals. The first group consisted of animals that underwent standard injury without any specific therapy. The animals were evaluated immediately before blast, 2 hours after blast (to allow recovery from anesthesia), and every 4 to 5 hours thereafter until death. The mean survival time of the animals in this group was 19.7 ± 5.4 hours (standard deviation).

The second group consisted of animals wounded by the standard technique and given penicillin therapy. Each animal received 300,000 units of procaine penicillin G and 1,000,000 units of crystalline penicillin G potassium one hour before injury, immediately after injury, and every 8 hours thereafter by intramuscular injection. The mean survival was 29.7 ± 12.0 hours (S.D.). The blood volume of the first two groups was not determined as frequently as the other values. A control volume was obtained before injury, a second determination performed approximately 8 hours after injury, and a third and final determination was made when the death of the animal appeared imminent.

The third group, consisting of 8 uninjured animals, restrained on carts, served as controls for the two foregoing groups. It was found that in the control goats the behavior was the same whether penicillin was administered or not, so that a single group served as valid control for both injured groups. After an initial observation, corresponding to the preblast study on the injured, a second was performed at the same time as a 2-hour postinjury observation. Periodic subsequent determinations were made every 8 hours for a total of 45 hours of observation. Blood volume was estimated at the time of the initial observation, 20 hours later, and at the conclusion of the study. In this way, the controls were handled in precisely the same manner as the injured groups with the omission of the massive injury. A standard hay-grain diet was administered to the goats until the beginning of the experiment. During the experiment all the animals were offered water periodically but no food. Because of the capacious gastric complex in this species (10 to 15 per cent of body weight with contents), lack of food for several days probably had no effect on any of the determinations under consideration in this report.

The changes observed in these parameters of cardiovascular function in the wounded animals were found to be more closely related to approaching death than to the time elapsed between injury and a particular observation. Therefore, observations were recorded as having taken place at a certain percentage of the total survival time of the animals under consideration. To

obtain a smooth curve, which could be considered as representative of the results from a group of animals, a graphical approach was utilized which is based on the method of advancing moments.[18] To establish the adequacy of this approach, the 0 (preblast), 20, 40, 60, 80, and 90 per cent points of the total survival time were examined, and residual variances were computed for these points.

Fig. 1 shows the correlation between successive estimations of the blood volume in 3 untreated and 4 penicillin-treated injured goats. When plotted against the absolute time elapsing after injury, as shown in the upper section, quantitative comparison between animals with different lengths of survival is difficult. The utilization of the percentage-of-survival method in the lower section, to compare quantities at different fractions of the survival period provides statistical simplification. In this figure the range of the survival time was 12.7 to 55.0 hours.

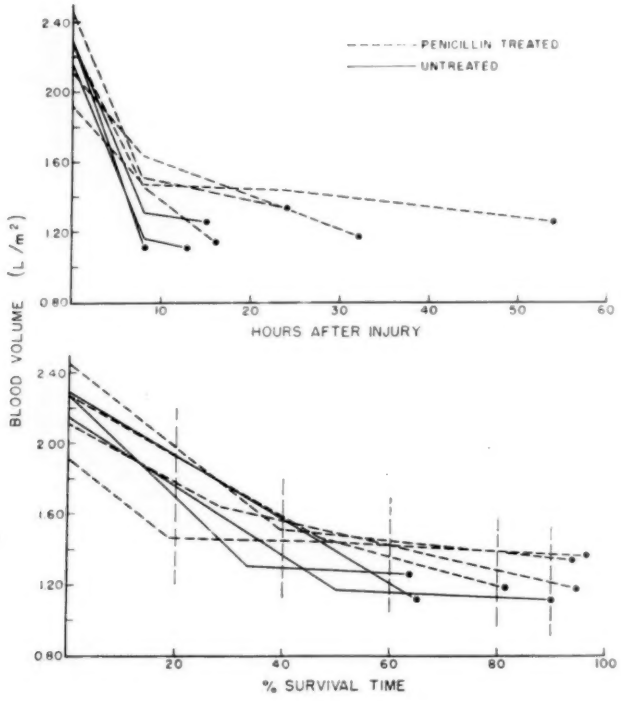

Fig. 1.—Change of blood volume in 7 animals, considered in relation to time after injury (*upper*) and to the percentage of survival time after injury (*lower*).

RESULTS

In order to interpret the changes induced by injury, the effect of maintenance in the restrained prone position must first be considered. Table I summarizes data obtained by observing 8 uninjured control animals. It will be noted that arterial and venous oxygen saturations do not change appreciably over the 45 hours of immobilization. There is a definite rise in pH in both arterial and venous blood. This is associated with a statistically insignificant rise in CO_2 content. Calculation of the pCO_2, by the nomogram developed by

Dill and associates,[9] reveals a fall in CO_2 tension. This indicates an incompletely compensated respiratory alkalosis. The mean minute volume of respiration is high throughout the observation period. This must be considered confirmatory evidence of the previously mentioned impression of respiratory alkalosis. There is a gradual rise in pulse rate. The cardiac index and mean arterial pressure show slight downward trends. The mean peripheral resistance shows no significant change. Also, blood volume and red cell mass decline slightly but not significantly. As suggested by the elevated pulse rate, the stroke volume decreases.

TABLE I. SERIAL VALUES OF EIGHT CONTROL ANIMALS*

DETERMINATION	HOURS ON CART						
	2	5	13	21	28	37	45
Arterial pH	7.42 ± 0.03	7.47 ± 0.04†	7.50 ± 0.02†	7.51 ± 0.04†	7.53 ± 0.03†	7.53 ± 0.02†	7.51 ± 0.04†
Venous pH	7.40 ± 0.02	7.44 ± 0.04†	7.45 ± 0.04†	7.47 ± 0.03†	7.50 ± 0.02†	7.48 ± 0.02†	7.47 ± 0.04†
Arterial O_2 saturation (%)	88.0 ± 3.1	90.3 ± 5.0	89.3 ± 5.0	84.9 ± 9.4	89.8 ± 8.7	92.2 ± 3.1	85.3 ± 6.5
Venous O_2 saturation (%)	61.0 ± 8.4	59.3 ± 11.4	54.0 ± 13.4	54.6 ± 11.2	55.3 ± 8.4	54.1 ± 7.7	51.9 ± 9.0
Arterial CO_2 content (vol. %)	44.6 ± 3.5	46.2 ± 2.9	46.6 ± 3.9	46.6 ± 5.2	47.8 ± 4.5	48.3 ± 4.1	47.4 ± 2.9
Venous CO_2 content (vol. %)	48.7 ± 3.7	50.5 ± 1.9	50.3 ± 3.5	51.6 ± 4.7	51.6 ± 3.6	52.4 ± 3.7	52.2 ± 4.8
O_2 consumption (ml./min./M.²)	214 ± 53	208 ± 44	214 ± 30	206 ± 31	201 ± 33	229 ± 59	224 ± 50
Minute volume (L./M.²)	6.16 ± 2.14	8.91 ± 5.94	6.05 ± 1.31	5.95 ± 1.74	6.33 ± 1.31	6.54 ± 1.34	5.71 ± 1.39
Pulse	92 ± 24	101 ± 15	107 ± 17	115 ± 18†	124 ± 18†	127 ± 16†	126 ± 18†
Mean arterial pressure	95 ± 19	86 ± 12	88 ± 10	90 ± 11	78 ± 12	80 ± 17	86 ± 10
Mean peripheral resistance	1.14 ± 0.47	1.11 ± 0.17	1.27 ± 0.27	1.31 ± 0.47	1.20 ± 0.40	1.23 ± 0.45	1.24 ± 0.39
Cardiac index (L./M.²/min.)	5.90 ± 1.61	5.16 ± 0.89	4.46 ± 0.78	5.02 ± 1.86	4.62 ± 1.60	4.52 ± 1.22	5.13 ± 1.68
Reduction		13%	24%	15%	22%	23%	13%
Blood volume (L./M.²)	2.10 ± 0.32			1.94 ± 0.17			1.89 ± 0.15
Reduction				7%			10%
Red cell mass (L./M.²)	0.56 ± 0.14			0.53 ± 0.13			0.52 ± 0.15
Reduction				6%			7%
Stroke volume (ml.)	62 ± 20	48 ± 10	39 ± 13†	43 ± 26	36 ± 16†	33 ± 11†	38 ± 14†
Reduction		23%	37%	31%	42%	47%	39%

*Each value represents mean ± standard deviation.
†Significance of change from initial observation (Student's t test), $p < 0.05$.

There appeared to be relative undersaturation of both arterial and venous blood of the control animals while on the carts. To investigate this feature further, an animal was evaluated under three varying conditions. Saturation was determined while the animal was on a cart and breathing air, on a cart and breathing O_2, and standing and breathing air. Poor oxygenation, despite a high minute volume of respiration, occurred when the animal was immobilized on a cart. The arterial O_2 saturation rose from 82 per cent to nearly complete saturation when the animal breathed O_2 while on a cart or air while standing. Venous O_2 saturation changed similarly so that the cardiac output did not change appreciably.

The data summarizing observations on 8 untreated injured animals are summarized in Table II. This group had a mean survival time of 19.7 ± 5.4 hours (S.D.) with a range of 12.8 to 26.6 hours. The respiratory response of these animals was similar to that of the controls, that is, an incompletely compensated respiratory alkalosis associated with hyperventilation. These changes are coincident with a typical shocklike vascular response. There was an immediate fall in O_2 consumption, cardiac output, mean arterial pressure, and stroke volume. The pulse and mean peripheral resistance became elevated immediately. The total blood volume and the red cell mass fell after injury at an equal rate. Because of difficulty in gauging the expected time of death, the last blood volume estimates in this group were usually taken several hours prior to death. For this reason only the rate of fall for the first 60 per cent of survival time could be computed. The blood volume seemed to fall at a greater rate initially than in the latter part of the postinjury survival period. The blood loss within the first 5 minutes of injury averaged only 133 ml. Subsequent reduction in estimated blood volume was not due to profuse external bleeding.

The data summarizing observation on 8 injured animals treated with penicillin are presented on Table III. These animals had a mean survival of 29.7 ± 12.0 hours (S.D.), with a range of 20 to 55 hours. The reason for the poor response of several animals of this group to penicillin treatment is not known. It had frequently been observed, however, that additional stress encountered in the methods described for these physiologic observations had a pronounced effect in reducing survival time. By treating all survival times in this group by the statistical simplification previously described, it is possible to consider each of these animals as having lived 30 hours. The general response in this group as judged by the various parameters employed was in many ways similar to the response of the untreated injured group. Hyperventilation associated with an incompletely compensated respiratory alkalosis was present. Cardiac output, O_2 consumption, mean arterial pressure, and stroke volume decreased in similar degrees. The rate of fall of the blood volume and of the red cell mass was approximately the same when considered in proportion to the total survival time. Thus, the penicillin-treated group had approximately the same percentage reduction in total blood volume at 40 per cent of the total survival period of 30 hours (12 hours) as did untreated

TABLE II. SERIAL VALUES OF EIGHT WOUNDED UNTREATED ANIMALS*
(Survival Time 19.7 Hours ± 5.4 Hours)

DETERMINATION	PERCENTAGE OF SURVIVAL TIME					
	CONTROL	20	40	60	80	90
Arterial pH	7.44 ± 0.02	7.45 ± 0.03	7.48 ± 0.04†	7.50 ± 0.05†	7.52 ± 0.07†	7.52 ± 0.10†
Venous pH	7.42 ± 0.03	7.40 ± 0.03	7.41 ± 0.03	7.43 ± 0.04	7.44 ± 0.07	7.43 ± 0.12
Arterial O_2 saturation (%)	87.3 ± 4.9	92.9 ± 5.9	91.5 ± 3.7	92.1 ± 4.0	87.8 ± 9.0	80.8 ± 20.6
Venous O_2 saturation (%)	58.7 ± 8.0	42.1 ± 7.7†	37.9 ± 8.9†	39.0 ± 12.8†	30.1 ± 13.5†	23.5 ± 13.1†
Arterial CO_2 content (vol. %)	41.5 ± 4.7	37.6 ± 6.3	40.8 ± 5.5	42.3 ± 4.7	39.0 ± 7.7	37.0 ± 10.0
Venous CO_2 content (vol. %)	46.8 ± 3.6	45.8 ± 4.5	48.3 ± 4.0	49.3 ± 4.4	46.8 ± 7.1	45.1 ± 8.6
O_2 consumption (ml./min./M.²)	194 ± 39	150 ± 31†	152 ± 30†	150 ± 28†	155 ± 28†	159 ± 31†
Minute volume (L./M.²)	7.32 ± 2.74	9.57 ± 3.50	8.37 ± 1.29	8.03 ± 1.84	11.01 ± 3.86†	12.24 ± 5.01
Pulse	94 ± 30	124 ± 13†	132 ± 11†	146 ± 7†	155 ± 14†	161 ± 22†
Mean arterial pressure	92 ± 12	58 ± 11†	56 ± 8†	56 ± 7†	53 ± 7†	51 ± 8†
Reduction		37%	39%	39%	42%	45%
Mean peripheral resistance	1.22 ± 0.34	1.74 ± 0.43†	1.77 ± 0.32†	1.84 ± 0.37†	1.86 ± 0.44†	1.81 ± 0.46†
Cardiac index (L./M.²/min.)	5.08 ± 1.77	2.21 ± 0.66†	2.21 ± 0.65†	2.17 ± 0.62†	2.09 ± 0.67†	2.06 ± 0.73†
Reduction		56%	56%	57%	59%	59%
Blood volume (L./M.²)	2.30 ± 0.33	1.90 ± 0.27†	1.55 ± 0.25†	1.29 ± 0.25†		
Reduction		17%	33%	44%		
Red cell mass (L./M.²)	0.54 ± 0.15	0.43 ± 0.11	0.34 ± 0.09†	0.28 ± 0.10†		
Reduction		20%	37%	47%		
Stroke volume (ml.)	55 ± 22	19 ± 6†	16 ± 4†	14 ± 3†	13 ± 3†	12 ± 3†
Reduction		65%	71%	75%	76%	78%

*Each value represents mean ± standard deviation.
†Significance of change from initial observation (Student's t test), $p < 0.05$.

injured animals at 40 per cent of the total survival period of 20 hours (8 hours). Later in the survival of the penicillin animals the rate of loss became somewhat less. The one major difference in the behavior of the two injured groups was the behavior of calculated mean peripheral resistance. Both groups showed a marked initial rise in resistance soon after injury. Over the remaining period of survival, however, the untreated animals maintained an elevated resistance, while in the longer-lived penicillin group the resistance gradually decreased. At 90 per cent of the survival time the latter group had a resistance equivalent to the preinjury value. At this period the divergent trends in peripheral resistance had a statistically significant difference ($p < 0.01$).

TABLE III. SERIAL VALUES OF EIGHT WOUNDED PENICILLIN-TREATED ANIMALS*
(Survival Time 29.7 Hours ± 12.0 Hours)

DETERMINATION	PERCENTAGE OF SURVIVAL TIME					
	CONTROL	20	40	60	80	90
Arterial pH	7.44 ± 0.04	7.50 ± 0.04†	7.53 ± 0.05†	7.55 ± 0.06†	7.56 ± 0.10†	7.55 ± 0.12†
Venous pH	7.41 ± 0.03	7.44 ± 0.04	7.48 ± 0.05†	7.50 ± 0.06†	7.50 ± 0.07†	7.50 ± 0.09†
Arterial O_2 saturation (%)	86.6 ± 5.1	89.3 ± 4.1	85.3 ± 6.0	84.8 ± 5.7	84.9 ± 8.7	82.8 ± 10.8
Venous O_2 saturation (%)	53.9 ± 7.1	30.9 ± 5.3†	28.6 ± 7.5†	28.4 ± 7.4†	31.1 ± 9.1†	28.3 ± 9.7†
Arterial CO_2 content (vol. %)	48.4 ± 6.4	47.3 ± 4.8	50.9 ± 6.6	52.6 ± 8.2	52.7 ± 9.0	51.0 ± 8.5
Venous CO_2 content (vol. %)	54.0 ± 6.4	54.7 ± 4.2	57.1 ± 6.1	58.0 ± 7.7	57.1 ± 9.3	54.8 ± 8.5
O_2 consumption (ml./min./M.²)	273 ± 43	189 ± 29†	197 ± 32†	203 ± 28†	188 ± 36†	187 ± 42†
Minute volume (L./M.²)	6.32 ± 1.41	9.50 ± 7.32	8.13 ± 2.63	6.58 ± 0.97	6.69 ± 1.81	6.38 ± 3.60
Pulse	98 ± 17	142 ± 18†	148 ± 16†	155 ± 17†	154 ± 21†	145 ± 12†
Mean arterial pressure	108 ± 11	67 ± 17†	70 ± 19†	70 ± 19†	67 ± 19†	60 ± 18†
Reduction		38%	35%	35%	38%	44%
Mean peripheral resistance	1.18 ± 0.36	1.67 ± 0.35†	1.54 ± 0.42	1.46 ± 0.40	1.37 ± 0.28	1.24 ± 0.20
Cardiac index (L./M.²/min.)	7.00 ± 1.78	2.64 ± 0.33†	3.23 ± 0.98†	3.40 ± 1.00†	3.25 ± 0.54†	3.34 ± 0.81†
Reduction		62%	54%	51%	54%	52%
Blood volume (L./M.²)	2.06 ± 0.26	1.72 ± 0.20†	1.45 ± 0.14†	1.35 ± 0.13†	1.28 ± 0.12†	1.24 ± 0.13†
Reduction		17%	30%	34%	38%	40%
Red cell mass (L./M.²)	0.54 ± 0.14	0.40 ± 0.10	0.30 ± 0.05†	0.27 ± 0.05†	0.26 ± 0.04†	0.25 ± 0.04†
Reduction		28%	46%	50%	52%	54%
Stroke volume (ml.)	66 ± 18	17 ± 3†	20 ± 7†	20 ± 7†	19 ± 3†	20 ± 4†
Reduction		74%	70%	70%	71%	70%

*Each value represents mean ± standard deviation.
†Significance of change from initial observation (Student's t test), $p < 0.05$.

Fig. 2 demonstrates the comparison of the more important aspects of cardiovascular function observed in these experiments in the untreated and penicillin-treated groups of injured animals.

DISCUSSION

Comparison of the two groups of injured animals with the uninjured control group yields two major similarities. The respiratory response of all animals was one of hyperventilation and a resultant partially compensated respiratory alkalosis. The calculated pCO_2 falls over the period of observation in all three groups, and is associated with a rising pH and slight elevation in

the CO_2 content in both arterial and venous blood specimens. It is apparent, therefore, that all of these groups are in a state of excitement. It seems likely that these effects of the nonbasal state might have been obviated in at least the controls by maintaining the animals under constant anesthesia. However, use of anesthesia is objectionable because of the effect on other features observed in these experiments. It has been shown that the circulatory response following hemorrhage affords less compensation in anesthetized than in unanesthetized animals.[38] Furthermore, the change in plasma volume resulting from the administration of Nembutal anesthesia may be appreciable.[14] For reasons such as these, it was considered preferable to tolerate certain problems caused by the absence of anesthesia, rather than the effects caused by its presence. It has been demonstrated in dogs that hemorrhage induces a response of hyperventilation and respiratory alkalosis,[2, 31] the stimulation arising reflexly in the chemo- and pressoreceptors of the aorta and carotid arteries.[34]

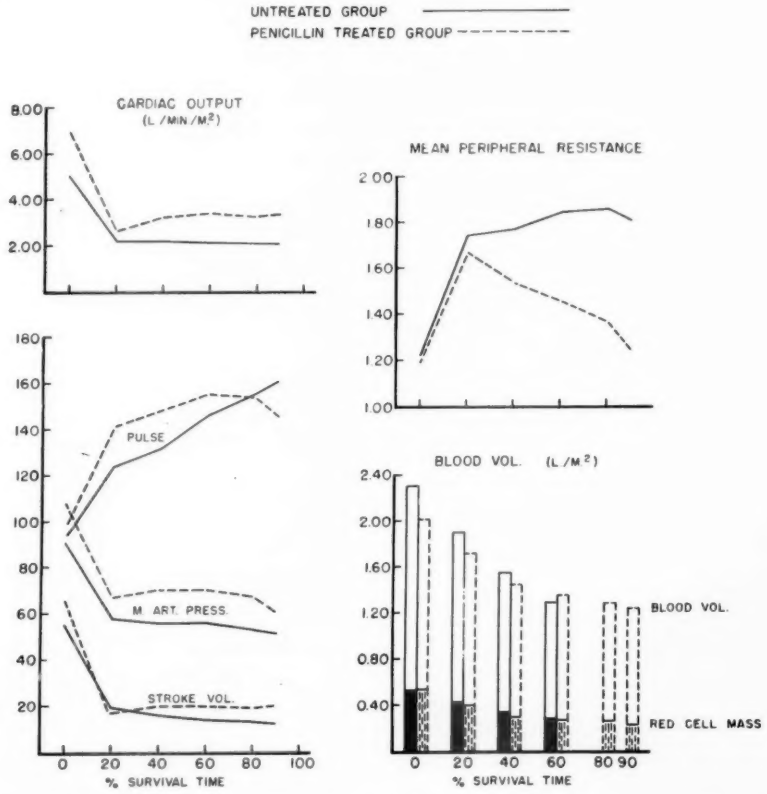

Fig. 2.—Graphical summary of important physiologic changes in injured animals. Each point represents the mean of eight determinations considered in relation to the percentage of survival time.

A second similarity, which appeared common to all three groups of animals, was the occurrence of relative undersaturation of the arterial and venous blood with oxygen in the presence of a concomitant hyperventilatory response. The hypoxemia, which is relieved either by the administration of oxygen to an animal lying in the cart or by permitting the animal to stand, is probably due to a disturbance of the ventilation/blood flow ratio in certain

areas of the lungs. Incipient atelectasis or compression of lung resulting from the restrained position could cause this phenomenon. With hyperventilation, CO_2 would be blown off but venous admixture would prevent full oxygen saturation.

The standard injury produced, in both the untreated and penicillin-treated animals, a profound and prompt shocklike state. The immediacy of this vascular response is considered striking in view of the gradual decrease in the estimated circulating blood volume. Similar findings were reported in the establishment of massive burns in dogs by scalding posterior portions of the body.[10] An intensive and sudden stimulation of neural receptors over a wide area of the hind portions has undoubtedly occurred in both types of experimental procedures. The immediate fall in cardiac output and blood pressure may occur on a neurogenic basis as a reaction to the massive stimulation caused by sudden injury. After a very short time, however, shock is unquestionably sustained by the mounting loss of blood and developing infection.

It is important to note that the penicillin-treated animals had, at 90 per cent of the elapsed survival time, an estimated circulating blood volume of 1.24 ± 0.13 L. per square meter (S.D.). The standard deviation is remarkably small in view of the fact that the range of survival times in this group was 20 to 55 hours. The terminal level of blood volume in the untreated animals was not computed because it was obtained in only 3 animals. If the estimate was obtained several hours prior to death, a relatively greater percentage of survival time remained because total survival was shorter. Until at least 60 per cent of the total survival time had elapsed, the two groups behaved very much alike in this regard. Thus, at the time of death, it may be inferred that approximately the same circulating blood volume per square meter of body surface area was present in all animals regardless of the duration of survival after injury (Fig. 1).

The enormous reduction in the estimated circulating blood volume after injury could not be predicted by observing the amount of blood lost externally from the wound. Of the 16 injured animals only one lost more than 150 ml. of blood at the time of injury, through hemorrhage from severed vessels before they were clamped. During the survival period, a variable amount of serosanguineous fluid oozed from the wound. The measured reduction in volume could not be correlated with visual estimates of the quantity of oozing. Since there is generally no increase of capillary permeability in the body after hemorrhage that permits exudation of blood,[13] most of this volume loss must be considered to have exuded into the area of injured tissue. This conclusion is supported by evidence from similar animal preparations.[3, 17]

After the initial fall in cardiac ouput, the output remains steady but at a low level in both groups of injured animals. There is no indication, short of the agonal state, that foretells the expected survival time of the animals. This does not mean that the heart may not have been damaged by the multiple severe stresses under which it was laboring. Biochemical studies of myocardial tissue from animals exposed to blood loss have shown marked losses

of intracellular sodium[32] and reduction of tissue oxygen consumption.[5, 15, 17] Also, because of decreased coronary artery perfusion occurring in shock,[7, 11, 33] there is a decrease in myocardial tone and, ultimately, dilation of the ventricles.[20, 21, 36] Structural alterations in mitochondria in ischemic myocardial cells have been reported,[35] as well as the occurrence of degenerative changes in myocardial tissue of animals recovering from exposure to a period of hemorrhage.[24] Apart from the factor of blood loss, the toxins of *Clostridium perfringens* have been shown to be toxic to myocardial tissue.[26] It is felt, however, that whatever myocardial damage occurred by subjection of the goat to a combination of blood loss, tissue trauma, and infection, there was no indication that the terminal event of death was caused by the single factor of gradual failure of the myocardium.

The mean peripheral resistance rose immediately after injury in both injured groups. In the untreated animals the mean remained elevated; in the penicillin-treated it fell back to approximately the preinjury level. The standard deviations of all these mean values were large and the results from each animal fluctuated considerably. For this reason, this particular statistic proved of no value in predicting the expected remaining survival of the injured animals.

The hemodynamic response of man to traumatic shock has been well documented.[4, 6, 8] Previous investigators have not been able to correlate any of the observed indices to establish prognostic significance. It has been shown that major wounds of the extremities are frequently associated with enormous reductions in blood volume.[12, 25, 30]

Long before the study of traumatic shock became a field of widespread interest, Gesell[16] pointed out that there are two phases in the natural history of the response of animals to shock. There are the initiating factors, represented by hemorrhage and the stress of massive sudden tissue destruction. These initiating factors are reinforced by sustaining factors. In the preparation represented by the hind leg injury in goats, these sustaining factors consist of continued loss of blood into the area of injured tissues and concomitant development of pathogenic clostridial infection in the wound. Both of these sustaining factors are injurious to the circulation. It therefore appears that since both blood loss and infection act to produce similar over-all results physiologically, distinction between the two, when both are active, is not possible by the methods used in these experiments. In the animals in which the effects of infection were reduced by the use of penicillin, and survival thereby prolonged, the general changes noted were of similar directions as those of untreated injured animals. In subsequent experiments, the relationship between the factors of clostridial infection and the loss of circulating blood volume will be defined further.

SUMMARY

Comprehensive studies of the respiratory and circulatory response of goats to standard experimental wounds were carried out in 8 control, 8 injured but untreated, and 8 injured, penicillin-treated animals.

The animals were all evaluated in a restrained position on carts. A respiratory alkalosis was present in all three groups.

The injured animals developed a typical shocklike response after injury, with reduction in arterial pressure, cardiac output, and stroke volume. None of the factors observed, except that of the rate of decrease of circulating blood volume, could be correlated with the survival time. The penicillin-treated animals had a mean survival time of 29.7 hours, the untreated animals a mean of 19.7 hours.

It was concluded that blood loss and infection of the wound with pathogenic clostridia act to produce similar over-all results physiologically. Distinction between the two, when both are active, is not possible by the methods used in these experiments.

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RENO-MESENTERO-AORTO-ILIAC THROMBOENDARTERECTOMY IN PATIENT WITH MALIGNANT HYPERTENSION

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IN RECENT years there has been mounting interest in the revascularization of ischemic organs (specifically the brain,[10, 18] lung,[22] heart,[1, 17] kidney,[7, 20] and intestine.[23] Early work on the direct surgery of occlusive arterial disease was focused on the lower extremities, not only because of the prevalence of involvement there, but because the symptoms of arterial insufficiency were clear-cut and methods of diagnosis were precise. In contrast, ischemia of visceral organs often resulted in vague symptoms, and diagnostic methods were frequently inexact. A further deterrent to reconstructive arterial surgery was the widely held view that major vessel occlusion to many visceral tissues would result in irreversible damage with such rapidity that reconstitution of arterial blood flow would be fruitless. It is now realized that this is often not the case and that all tissues of the body (under the appropriate circumstances) may react to extensive devascularization with diminished function rather than by necrosis.

The present report documents a case in which there was interference with the major arterial supply of both kidneys as well as partial occlusion of the superior mesenteric artery—complicating an extensive aortoiliac thrombosis. The patient presented with intermittent claudication, malignant hypertension, abdominal pain, and rapid weight loss. Treatment consisted of thromboendarterectomy of all involved vessels, with relief of the cardiovascular and gastrointestinal complaints.

CASE REPORT

W. J. (USVAR 23482), a 62-year-old white man, had been in a mental institution (with a diagnosis of schizophrenia) for 19 years prior to the present admission on Oct. 2, 1958. Occasional blood pressure determinations were normal until late 1955 when he was noted to be hypertensive (blood pressure 200/100 mm. Hg). Subsequently, the hypertension progressed despite drug therapy. During the first 9 months of 1958 blood pressures ranged from 200/90 to 300/160 mm. Hg. During the 6 months preceding admission he had developed severe headaches, sporadic chest pain, and intermittent claudication. During the 6 weeks preceding admission he had lost 30 pounds, and had developed constipation and remittent abdominal pain (provoked by eating). ECG was normal until March, 1958, when a left ventricular strain pattern was first noted.

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Physical Examination.—This was a well-developed, withdrawn white man who appeared chronically ill. Blood pressure was 220/100 to 300/160 mm. Hg during the preoperative period (Fig. 1, *A*); pulse rate was 80 to 100. Ophthalmoscopy showed blurring of both discs, bilateral retinal hemorrhages, and extreme arteriolar narrowing. The apical heartbeat was in the sixth intercostal space, 11 cm. from the midline. Running inferomedially from the lower anterior chest to the abdomen were pulsating serpiginous collaterals. Similar vessels, some as large as lead pencils, were also in the lower abdomen. The abdominal aorta could be palpated in the epigastrium, but no lower. A very feeble right femoral pulse was detectable (subsequently shown to be due to collateral flow), but there were no other pulses in either leg. On rectal examination, pulsating collaterals could be felt on the surface of the prostate.

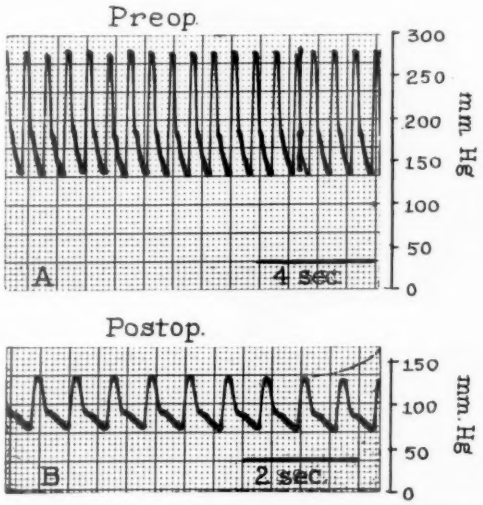

Fig. 1.—Direct brachial artery blood pressures before (*A*) and 9 weeks after (*B*) surgery.

Laboratory Studies.—Hemogram and coagulogram were normal. Urinalysis was normal except for a few hyaline casts; specific gravity 1.015. Blood urea nitrogen was 15. Fasting blood sugar, serum proteins, Bromsulphalein, prothrombin time, and Wassermann test were normal. There was slight cardiomegaly on chest x-ray and ECG showed left ventricular hypertrophy. Analysis of 3-day stool specimen revealed total daily fecal fat of 2.3 grams, neutral fat of 1.9 grams, and fatty acids of 0.66 gram per day. Aortogram (50 per cent Hypaque) on Oct. 16, 1958, revealed complete thrombosis of the abdominal aorta with nonvisualization of the left renal artery and stenosis at the origin of the right renal artery (Fig. 2). The aortic occlusion began just at the mouth of the superior mesenteric artery (Fig. 2), but this vessel filled with dye.

Renal Function Studies.—Prior to aortography, a number of renal function studies were done. Blood urea nitrogen was 15 mg. per cent. Intravenous pyelogram was reported as normal with good excretion bilaterally. Phenolsulfonphthalein (PSP) excretion was 13, 13, 14, and 13 per cent at 15, 30, 60, and 120 minutes (total 53 per cent). Urea clearance during diuresis was 33 (about 40 per cent of normal). Radioactive Diodrast renograms were interpreted as showing a comparatively reduced vascular phase on the left.

Split functions during diuresis were determined (Table I) after bilateral ureteral catheterization.[6] These showed a marked reduction in volume, sodium concentration, and phenolsulfonphthalein excretion on the left as compared to the right.

Course in Hospital.—On Oct. 17, 1958, exploration was carried out under systemic hypothermia (31° C.), attained with a combination of blanket and intragastric balloon cooling.[12] A thoraco-abdominal incision was employed with a midline abdominal component extended into the eighth intercostal space. The femoral arteries were exposed

TABLE I. SPLIT RENAL FUNCTIONS

DETERMINATION	RIGHT KIDNEY	LEFT KIDNEY	BLADDER
Preoperative			
30-minute volume	40 c.c.	7 c.c.	9 c.c.
30-minute PSP	25%	4.5%	
Sodium concentration	54 mEq./L.	28 mEq./L.	13 mEq./L.
Postoperative (12 weeks)			
30-minute volume	35 c.c.	20 c.c.	0
30-minute PSP	23%	11%	
Sodium concentration	44 mEq./L.	89 mEq./L.	

in the femoral triangle. The spleen, stomach, pancreas, and left colon were reflected to the right. The common iliac arteries, aorta, celiac axis, superior mesenteric artery, and both renal arteries were encircled with tapes. The superior mesenteric artery and celiac axis pulsated, the former somewhat weakly. The left renal artery did not pulsate and in the proximal 1.5 cm. was not compressible. Distal to the origin of the right renal artery a sharp thrill was palpable, and pulsations were weak.

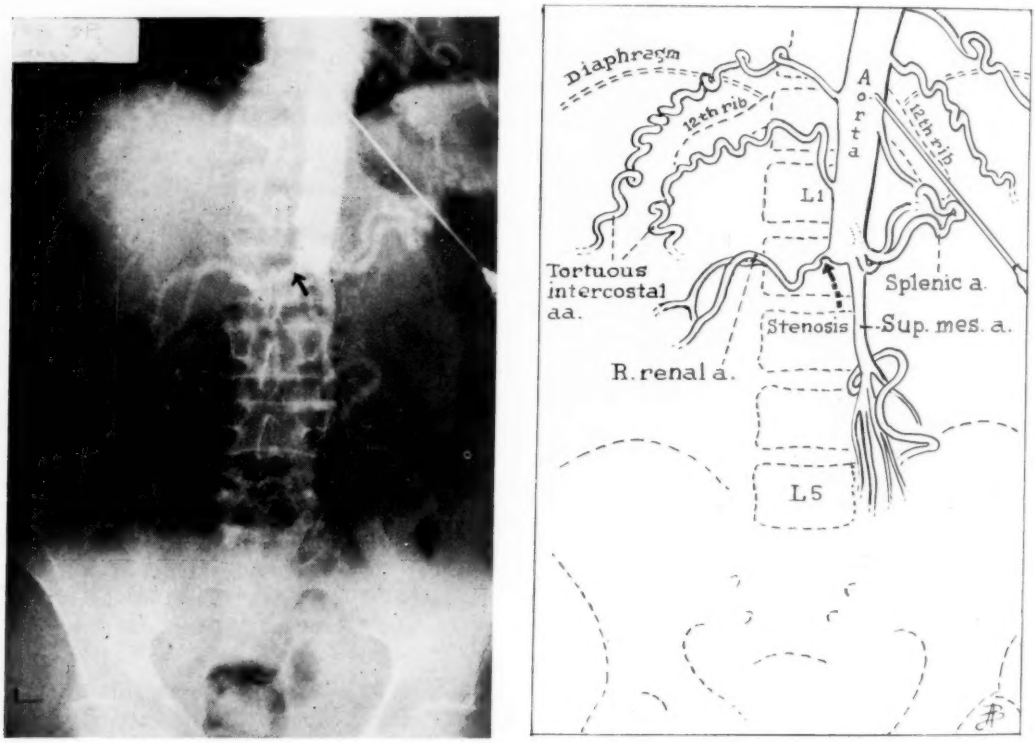

Fig. 2.—Preoperative aortogram.

Distal thromboendarterectomy was carried out first, from the superficial femoral arteries to the aorta, with strippers placed through incisions in the common femoral and common iliac arteries. An anterior aortic incision was then made and the iliac thrombi were extracted superiorly (Fig. 3). The linear aortic incision was extended superiorly above the origin of the superior mesenteric artery and the occluding core was removed in retrograde fashion. The cleavage plane in the media was well developed. When the level of the renal vessels was reached the aorta was cross-clamped (for a total period of 40 minutes) below the celiac axis and above the superior mesenteric artery. The

superior mesenteric artery was similarly cross-clamped to prevent back-bleeding. Endarterectomy of the left renal artery was then carried out from the aortic interior with a combination of gentle traction on the firm thrombus, distal traction on the renal artery adventitia, and development of the endarterectomy plane with the spatula (Fig. 3).

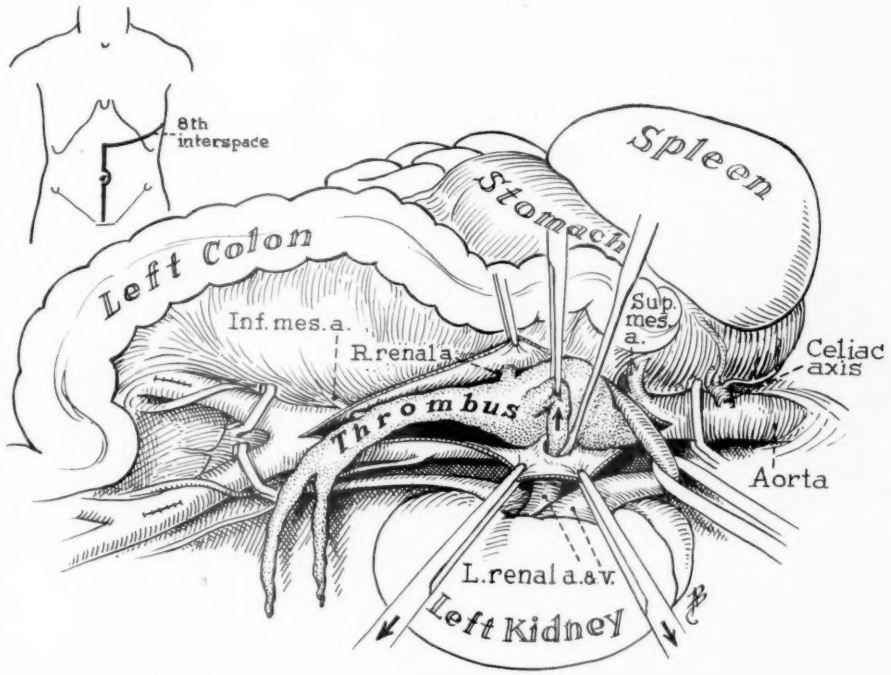

Fig. 3.—Transaortic left renal thromboendarterectomy.

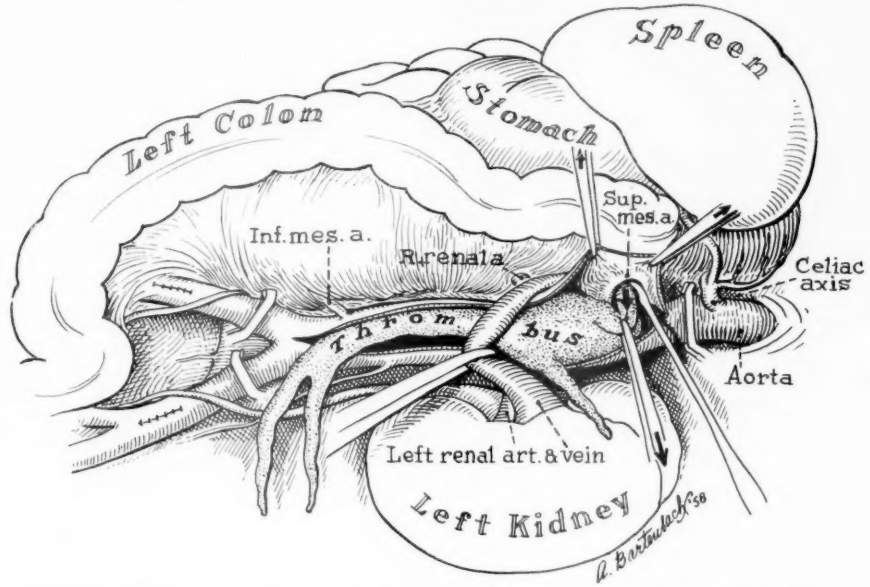

Fig. 4.—Transaortic thromboendarterectomy of superior mesenteric artery.

Endarterectomy was carried distally 1.5 to 2 cm. before the specimen broke off at a point where a lumen was present and where the intimal layer seemed delicate. Back-bleeding was brisk. The aortic specimen was then rolled to the left, and it was seen

that there was infringement on the orifice of the superior mesenteric artery by the proximal end of the aortic thrombus. Superior mesenteric thromboendarterectomy was consequently done on the proximal 1 cm. of this vessel (Fig. 4). Finally a similar transaortic thromboendarterectomy was done on the proximal 1.5 cm. of the right renal artery, following which there was good backflow from this vessel.

The aortic thromboendarterectomy was then terminated just below the celiac axis and the specimen was removed. A firm gray-white ligneous thrombus had completely occupied the lumen of the aorta starting 1 cm. below the renals and extending to the origin of both external iliacs (Fig. 5). Above this a soft brown (apparently more recent) thrombus extended for 2 cm., occluding and extending into the left renal artery and partially occluding the right renal as well (Fig. 5). The proximal end of the thrombus was at the level of and partially occluded the superior mesenteric artery (Fig. 5).

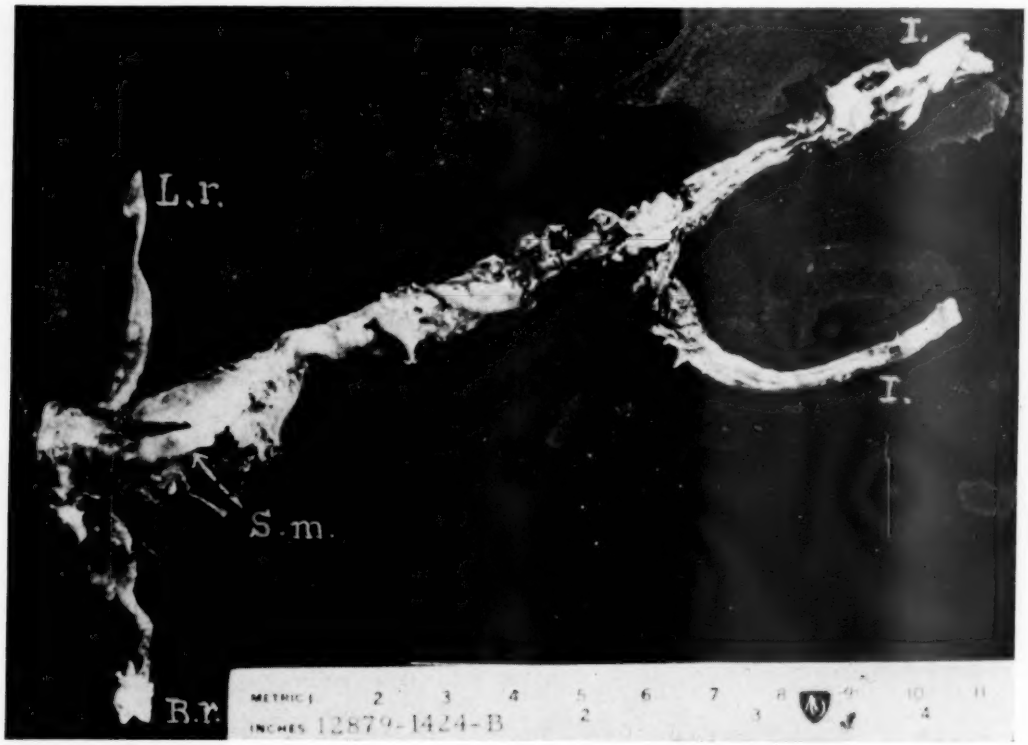

Fig. 5.—Thromboendarterectomy specimen. (*R.r.*) Right renal; (*L.r.*) left renal; (*S.m.*) superior mesenteric; (*I*) iliac.

The long aortotomy was closed and blood flow was re-established to the lower half of the body. After some minutes the left external iliac artery clotted at a place where the adventitia was injured during thromboendarterectomy, and it was necessary to replace this segment with a pre-clotted knit Teflon graft. When blood flow was re-established, bleeding through the wall of the prosthesis was excessive and did not cease for almost a half hour. The wounds were then closed. Tracheotomy was performed at the conclusion of the procedure,[24] and the patient was taken to the recovery room. Blood replacement (10,000 c.c.) had been necessary during the operation. As the abdomen was being closed, diuresis started, and 1,000 c.c. of urine was eliminated during the next 2 hours.

During the first postoperative night evidence of intra-abdominal bleeding developed, necessitating 10 more transfusions during the first 14 postoperative hours. Blood samples on October 18 did not clot in 24 hours. The abdomen was then re-explored on October

18 and multiple small bleeding points in the retroperitoneal space were ligated. Splenectomy was performed, and the abdomen was drained and closed. Subsequently slow bleeding into the peritoneal cavity continued for 48 hours and then ceased. On the second, third, and fourth days brisk gastrointestinal hemorrhages occurred. Additional transfusions during this period increased total blood replacement during and after operation to 44 units.

After one week, the patient resumed oral intake. The tracheostomy was removed in 10 days. Blood urea nitrogen rose steadily to 144 mgm. per cent during the first 10 days and then declined to 16 mgm. per cent by the twenty-fifth postoperative day. For the first 4 days after the second operation, oliguria was present (400 to 600 c.c. per day) but after this diuresis of about 2,000 c.c. daily continued for more than 2 weeks. Electrolytes remained normal throughout. All peripheral pulses in the legs have remained palpable. The abdominal wall collaterals disappeared almost immediately after surgery.

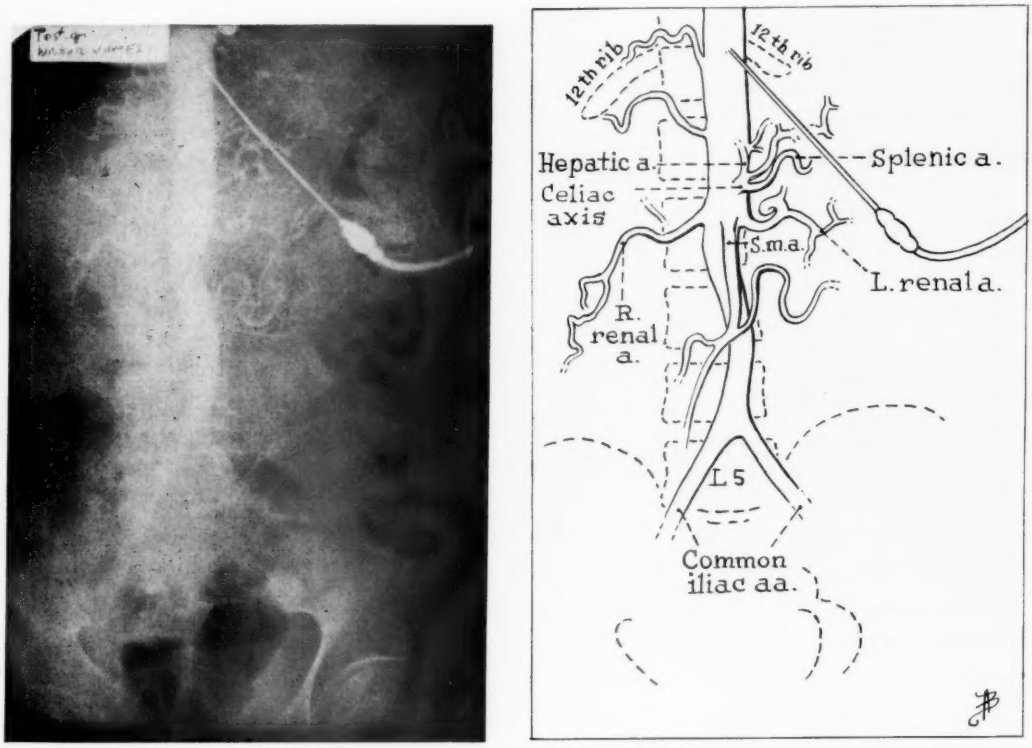

Fig. 6.—Postoperative aortogram (9 weeks).

After the immediate postoperative convalescence, his condition remained good. The preoperative complaints of chest pain, headache, intermittent claudication, and abdominal pain were not present. He was kept in the hospital for psychiatric care for several months, and was discharged to the mental institution from which he came on Feb. 25, 1959, 4½ months postoperatively.

Postoperative Laboratory Studies.—Chest x-ray revealed regression of the cardiomegaly within one month. ECG 2 months postoperatively was normal. Daily fecal fat content (3-day collection) was 1.16 Gm. 2 months after operation. Aortogram (Fig. 6), 9 weeks postoperatively, showed good filling of the aorta, celiac axis, both renal arteries, superior mesenteric artery, and iliac arteries.

Postoperative Renal Function Tests.—Blood urea nitrogen determinations after the first 3 postoperative weeks ranged from 10 to 15 mgm. per cent. Phenolsulfonphthalein excretion 2 months after operation was 10, 12, 22, and 12 per cent at 15, 30, 60 and 120

minutes (total 56 per cent). Split renal functions 3 months postoperatively revealed a marked comparative increase in sodium concentration, PSP excretion, and volume from the left kidney.

Effect on Blood Pressure.—By the end of the third postoperative day, the blood pressure was established at normotensive levels (Fig. 1, *B*). Readings were obtained every 4 hours during the remainder of the hospitalization, and no sustained elevation was ever noted. The average blood pressure during the third, fourth, and fifth postoperative months was 126/84 mm. Hg. The highest individual pressure during this 10-week period was 160/100 mm. Hg.

DISCUSSION

The first case of Goldblatt hypertension successfully treated with reconstructive arterial surgery was reported by Freeman and co-workers[11] in 1954. Subsequently, a small number of patients with either congenital or arteriosclerotic renal artery occlusion have been treated with excision of the stenosis and re-anastomosis or homograft,[7, 13, 20] splenorenal arterial anastomosis beyond the occlusion,[7, 14] or renal thromboendarterectomy.[7, 13] Of particular interest was Poutasse's patient[21] who had bilateral renal artery stenosis corrected with a homograft first on one side and then the other (14 days later). There was no gross deviation from the pre-existing urinary function after either procedure, but ureteral catheterization studies shortly after each operation showed an increase in sodium concentrating ability first on one side and then the other.

Until the present report the only other patient with bilateral renal artery occlusion relieved at one stage was described by Castillo and Barrera.[5] In this case a fresh thrombus formed proximal to a pre-existing chronic aortic occlusion, closing the mouths of the renal vessels. Treatment consisted of extraction of the fresh aortic thrombus without treatment of the chronic distal occlusion. In contrast to the present case, the thrombus did not extend into the renal arteries, and no other treatment of these vessels was necessary. It is interesting that in this case, as in ours, there was immediate striking diuresis which started as the abdomen was being closed. A similar but less extensive case has been reported by Cannon[3] in which an aortic thrombus which involved the renal arteries was extracted from below.

So much has been written about the clinical characteristics[6, 7, 19] and laboratory diagnosis[6, 7, 20] and of Goldblatt hypertension that it would be purposeless to review the matter here. In this patient, it was clear from differential function tests that the left kidney had a much greater functional impairment than the right. Since these tests depend on the comparison of an abnormal kidney to the opposite normal organ, it is impossible to quantitate the degree of impairment of the better kidney in a case such as the one described. The diagnosis must be made by aortography and confirmed at surgery as previously pointed out by Poutasse.[20]

After the aorta had been opened in this patient, a high degree of occlusion of the superior mesenteric artery was found. This vessel had been visualized well on the aortogram and pulsated on external examination. Endarterectomy on this vessel was carried out partly because clean removal of

the adjacent aortic occlusion was not otherwise possible, and partly because some of the preoperative complaints (vague abdominal pain aggravated by eating, rapid weight loss) were suggestive of "intestinal angina." These symptoms have been absent since operation.

Information concerning the effect of slow occlusion of the splanchnic blood supply has accumulated during the last 20 years. It is known experimentally that gradual occlusion of the celiac axis and/or superior mesenteric arteries may not result in bowel necrosis,[2, 16] that many cases of massive mesenteric infarction due to slow occlusion of the blood supply are preceded by weeks or months of premonitory symptoms,[9] and that the diseased portion of the superior mesenteric artery is almost always confined to the mouth or first 2 cm.[4, 8] A clinical syndrome of relative arterial insufficiency of the bowel has crystallized,[15, 23] and recently 2 patients with "intestinal angina" and subsequent frank small bowel infarction have been successfully treated with superior mesenteric thromboendarterectomy.[23] The present case is thought to represent the third instance of successful relief of mesenteric insufficiency.

SUMMARY

1. A case is documented in which there was complete occlusion of the left renal artery and partial occlusion of the right renal and superior mesenteric arteries, complicating extensive aortoiliac thrombosis.

2. The patient presented with malignant hypertension, intermittent claudication, and abdominal complaints suggestive of "intestinal angina."

3. Treatment consisted of thromboendarterectomy of all involved vessels, following which the patient became normotensive and had cessation of the abdominal symptoms.

4. The case is thought to be the first successful bilateral simultaneous renal endarterectomy, and the third successful case of superior mesenteric endarterectomy.

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FAILURES OF HOMOGRAFTS AS ARTERIAL REPLACEMENTS

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THERE has been a renewed interest in the direct surgical approach for the treatment of arterial disease during the past 10 years, which has made it necessary to develop adequate materials to use as replacements for blood vessels. The most popular materials used have been arterial homografts, autogenous veins, and synthetic prostheses.

Homografts have probably been the most widely used replacements. Several reported experiences with large numbers of homografts have included discussions of complications.[1, 7, 13, 14, 19] An increasing number of case reports of homograft complications have also appeared.[8-11, 16, 18] These reports have prompted us to scrutinize closely the fate of 90 homografts which have been used from the Blood Vessel Bank at Strong Memorial Hospital from May, 1955, to May, 1958. Some complications which were observed would have occurred with the use of any type of arterial replacements. However, there were 8 complications directly attributable to the use of homografts as the arterial replacements, which form the basis of this report.

METHODS

The homografts were obtained from patients under 45 years of age who died following trauma or nonmalignant and noninfectious diseases. They were removed under sterile conditions and stored for 24 to 48 hours in a saline solution which contained penicillin and streptomycin. They were then frozen with liquid nitrogen (boiling point of –193° C.) and then stored at a temperature of –18° C. until used.[17] Bacteriologic studies were made when the homograft was obtained, following sterilization, and at the time it was used. Pathologic studies were performed on each specimen at the time it was obtained and just before use (post thawing.) The purposes for which the homografts were used are recorded in Table I.

TABLE I. CLINICAL USES OF 90 FROZEN HOMOGRAFTS

Aortic bifurcation replacements	42
Femoral artery replacement—as shunt grafts	35
Peripheral aneurysm replacement	3
Traumatic arterial injury replacements (peripheral vessels)	5
Aortopulmonary artery shunts	3
Descending thoracic aorta replacement	2
Total	90

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Postoperatively, the patients were re-evaluated periodically. Postoperative arteriograms were obtained, in general, only at the time of change in clinical status of the limb. Direct examinations of the homografts were made in some instances at the time of re-exploration. Twenty-six of the homografts became available for pathologic study because of death of the patient or amputation of a limb.

HOMOGRAFT FAILURES

Eight complications occurred which seem to be related directly to the choice of a homograft as the material for arterial replacement. These do not include complications due to technical errors such as hemorrhage from suture lines or progression of disease in the host artery which may occur with the use of venous autografts, or synthetic prostheses, as well as homografts. These eight complications and similar reported cases are summarized in Table II.

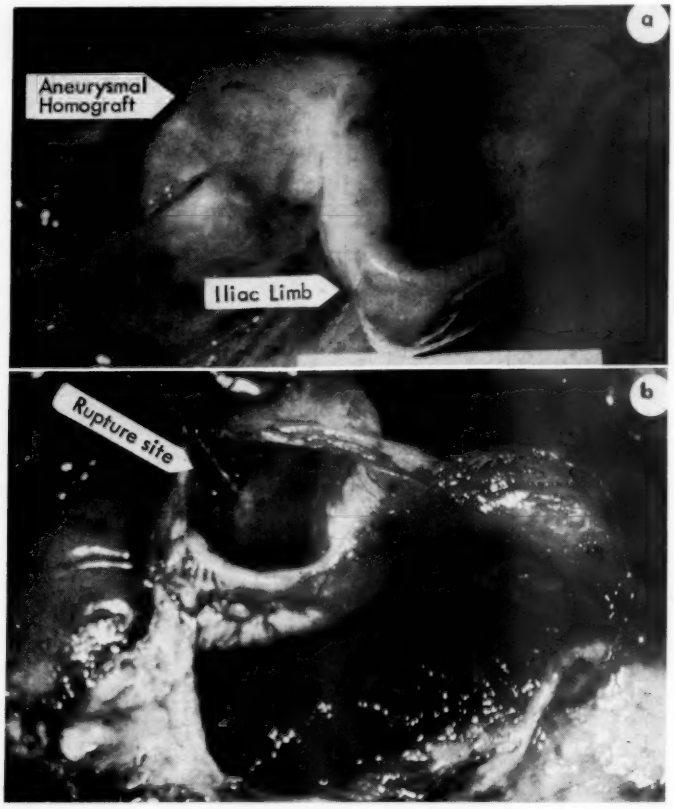

Fig. 1.—Case 1. The appearance of the aneurysmal homograft and its tortuous iliac limb is seen in *a*. The graft was then dissected free and elevated to expose the posterior rupture site which had resulted in erosion of the lumbar vertebrae in *b*.

Aneurysms.—

CASE 1.—A 47-year-old man, with arteriosclerotic and thrombotic occlusion of the left common iliac artery and marked narrowing of the right common iliac artery, had a resection of the terminal aorta and proximal iliac arteries with replacement of a frozen aortic bifurcation homograft on Aug. 2, 1955. About 12 months postoperatively the patient developed back pain. Radiographs of the lumbar spine revealed erosion of the third and fourth lumbar

vertebrae. On Nov. 9, 1956, 15 months following his original operation, he suddenly developed severe abdominal pain, vomiting, and shock, and died before surgical exploration could be performed.

At autopsy, a posterior aneurysmal dilatation, 5 cm. in diameter, of the aortic portion of the homograft was found (Fig. 1). The aneurysm caused erosion of the third and fourth lumbar vertebrae, and ruptured posteriorly, eventually resulting in massive hemorrhage into the retroperitoneal tissue and peritoneal cavity. Microscopically there was marked loss of elastic fibers and foci of mucoid degeneration in the entire graft, particularly the region of the aneurysm.

CASE 2.—A 60-year-old man with an occlusion, 1 cm. long, of the femoral artery at the level of the adductor hiatus had an end-to-side bypass procedure using a frozen homograft on Jan. 3, 1956. On Jan. 15, 1957, 12 months following operation, a femoral arteriogram revealed aneurysmal dilatation of the homograft (Fig. 2). Another arteriogram on March 27, 1957, revealed some progression in dilatation and possible partial thrombosis. On May 6, 1957, 16 months following operation, complete occlusion of the homograft and distal thrombosis occurred necessitating a left mid-calf amputation on May 15, 1957, despite the successful placement of an autogenous vein bypass around the thrombosed graft.

Fig. 2.—Case 2. The dilated homograft with a central aneurysm is pictured. This aneurysm was first noted 12 months after operation.

CASE 3.—On Jan. 14, 1956, a 55-year-old man with a popliteal aneurysm had a bypass procedure from the mid superficial femoral artery to the posterior tibial artery, utilizing a frozen homograft. A femoral arteriogram performed March 25, 1957, 14 months following operation revealed aneurysmal dilatation of the homograft (Fig. 3). Another arteriogram made on Aug. 12, 1957, showed progression in the dilatation and tortuosity On Sept. 12, 1958, 32 months following operation, the patient developed sudden numbness and coldness of the left foot, with marked evidence of arterial insufficiency. The leg remained viable with a conservative regimen of a sympathetic block, heparinization, and lumbar sympathectomy. An arteriogram revealed thrombosis of the graft and also of the popliteal and distal vessels.

TABLE II. REPORTED COMPLICATIONS ATTRIBUTABLE TO THE USE OF A HOMOGRAFT AS AN ARTERIAL REPLACEMENT

COMPLICATION	AUTHOR	SITE OF GRAFT	PRESERVATION	TIME NOTED POSTOPERATION	ADDITIONAL REMARKS
Aneurysms	Humphries et al.	Femoral artery	Freeze-dried	8 months	Arteriosclerosis in graft; replaced successfully
	Gwathmey and Thompson	Thoracic aorta	Freeze-dried	4 months	Kinked; medial degeneration; replaced successfully
	Szilagyi et al.	Abdominal aorta	? Fresh ? Freeze-dried	30 months	--
		Abdominal aorta	? Fresh ? Freeze-dried	36 months	Multiple
		Iliac artery	? Fresh ? Freeze-dried	7-12 months	--
		Iliac artery	? Fresh ? Freeze-dried	13-24 months	--
		Femoral artery	? Fresh ? Freeze-dried	11 months	--
	Jamplis et al.	Abdominal aorta	Freeze-dried	11 months	Degeneration elastic fibers; ruptured and died
	Susman	Abdominal aorta	--	11 weeks	Multiple; ruptured and died
	Hershey et al.	Abdominal aorta	? Freeze-dried ? Frozen irradiated	--	At site of ligated hypogastric artery; died
	Present series	Abdominal aorta	Frozen	12 months	Degenerated elastic fibers; ruptured and died
		Femoral artery	Frozen	12 months	Thrombosis; replaced with vein graft; amputation
		Femoral artery	Frozen	14 months	Thrombosis; conservative regimen preserved the limb
Rupture	Hamblin and Lord	Abdominal aorta	B.E.S. 2°-4° C.	8 days	Fragmented elastic fibers; died
	Humphries et al.	Abdominal aorta	Freeze-dried	15 days	Abdominal incision grossly infected; died
		Abdominal aorta	Freeze-dried	12 days	Rupture in iliac limb at site of constriction by horseshoe kidney; died
	Barnes et al.	Abdominal aorta	Ringer's, serum, Merthiolate. 2°-4° C.	8 days	Cystic medial necrosis; new graft placed; died
		Abdominal aorta	Ringer's, serum, Merthiolate. 2°-4° C.	6 weeks	Rupture of mid-portion of graft; died

	Foster et al.	Abdominal aorta	Freeze-dried	21 days	Rupture at bifurcation; surrounding suppurative changes present; died
		Abdominal aorta	Freeze-dried	6 days	Necrosis with rupture left common iliac
	Gaspar	Abdominal aorta	Freeze-dried	4 days	Defect in homograft; medial necrosis; intimal split; replaced successfully
		Abdominal aorta	Freeze-dried	At operation	Intimal split; died
		Abdominal aorta	Freeze-dried	At operation	Longitudinal split anterior wall
		Popliteal	Freeze-dried	5 days	Longitudinal split
	Gerbode	Aorta	--	3-4 days	Slit in graft
		Aorta	--	--	Tie blew off intercostal vessel
	Present series	Abdominal aorta	Frozen	3 hours	Rupture of site of arterial branch; died
Rupture into the intestine	Barnes et al.	Abdominal aorta	Ringers, serum, Merthiolate 2°-4° C.	16 months	False aneurysm anterior graft ruptured into duodenum; died
	Present series	Abdominal aorta	Frozen	11 months	Rupture site of arterial branch into jejunum; died
		Abdominal aorta	Frozen	26 months	Rupture site of arterial branch into jejunum; died
Thrombosis	Szilagyi et al.	Femoral	? Fresh ? Freeze-dried	6 months	Defect mid-graft at site of suture
		Femoral	? Fresh ? Freeze-dried	3 months	Defect mid-graft at site of suture
		Femoral	? Fresh ? Freeze-dried	3 months	Primary thrombosis of graft
	Hershey et al.	Femoral	? Freeze-dried ? Frozen-irradiated	At operation	Unrecognized placques and narrowing of graft
		Femoral	? Freeze-dried ? Frozen irradiated	At operation	Intimal tears
	Present series	Femoral	Frozen	6 months	Primary thrombosis of graft
Infection	Present series	Femoral	Frozen	5 days	Resulted in thrombosis; septicemia and death

Comment.—These cases represent the failure of homografts because of their inability to retain or develop satisfactory tensile strength. The failure in Case 1 was due to an abnormal degeneration of elastic fibers. The degeneration seemed abnormal in this instance since we have observed other homografts which were implanted for even larger periods which did not show such marked sparsity of elastic fibers. The homografts in Cases 2 and 3 did not become available for pathologic study. Microscopic sections of portions of these grafts prior to their use did not reveal abnormalities to suggest that these grafts would fail.

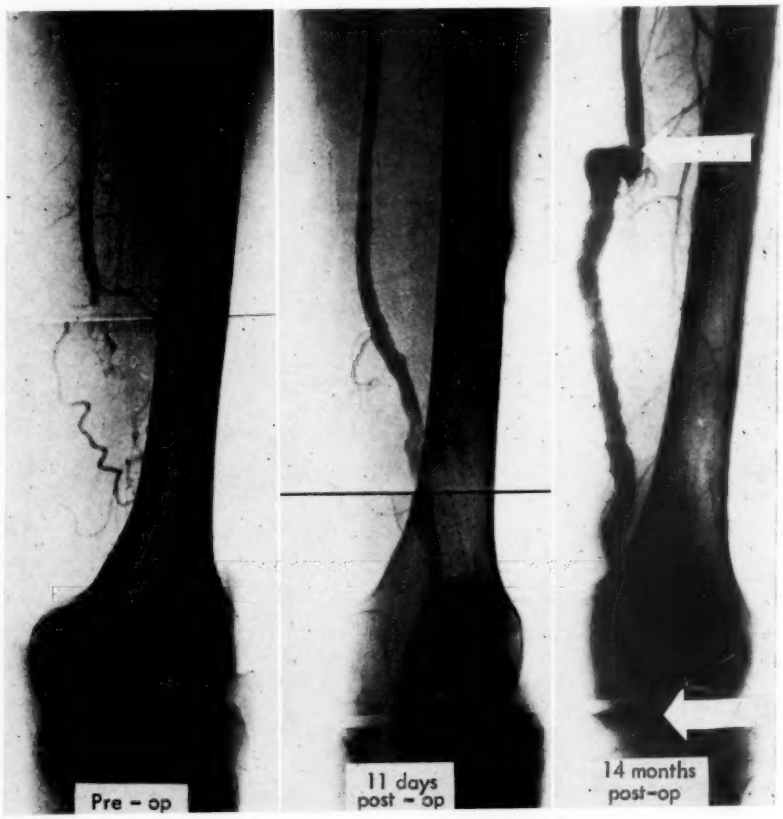

Fig. 3.—Case 3. The preoperative film indicated the long block of the popliteal artery. At 11 days after operation, the functioning arterial homograft was visualized. Fourteen months after operation, the homograft (between *arrows*) was dilated, tortuous, and aneurysmal just distal to the proximal anastomosis.

The failure of the aortic homograft (Case 1) was directly responsible for the patient's death. Thombosis of the aneurysmal femoral homografts or progression of disease resulted in amputation in Case 2 and morbidity in Case 3.

Rupture.—

CASE 4.—A 67-year-old man, with an abdominal aortic aneurysm, had the abdominal aneurysm and bifurcation resected and replaced with a frozen homograft on May 2, 1957. The patient went into shock about 3 hours postoperatively which temporarily responded to blood transfusion. Shock recurred and the patient was returned to the operating room where a small hole on the anterior wall of the homograft about 3 cm. below the proximal

anastomosis was found and sutured. The patient died during the operation. At autopsy the hole was shown to be at a site where an arterial branch had been sutured during preparation of the homograft. Microscopic study of the homograft revealed it to be otherwise a satisfactory graft.

Comment.—This case represents a failure of a homograft because of inherent technical difficulties in the use of homografts. Although suture ligatures were placed at the base of the arterial branches of the homograft, the rupture occurred at this site. Either the base of the vessel proximal to the suture ligature had been torn at the time the graft was obtained or the suture ligature had been inadequately placed or tied at the time the graft was prepared. Although this is technically a human error it is not the type of mistake which could be made with the use of a synthetic prosthesis and, therefore, it is considered a failure of the homograft which resulted in the death of the patient.

Rupture Into Intestine.—

CASE 5.—On Sept. 18, 1956, a 74-year-old man with an aneurysm of the abdominal aorta had the aneurysm resected and replaced with a bifurcation aortic frozen homograft, and covered with parietal peritoneum. The patient was discovered to have a duodenal ulcer postoperatively. He was readmitted on Aug. 20, 1957, 11 months following his operation with massive gastrointestinal bleeding. An exploratory laparotomy failed to establish the site of bleeding and the patient died on Aug. 26, 1957.

At autopsy a fistula between the aortic homograft, 3 cm. distal to the proximal anastomosis, and the distal jejunum was discovered. There were dense adhesions in the region. Microscopic sections of this region revealed disruption of the wall of the homograft at the site of the fistula (Fig. 4). However, there were abundant intact elastic fibers without fragmentation extending to the very border of the defect suggesting that this area was probably the site of a ligated arterial branch.

CASE 6.—A 54-year-old man, with an abdominal aorta aneurysm, had the aneurysm resected and replaced with an abdominal aortic frozen homograft on April 26, 1956. The patient noted recurrence of intermittent back pain in December, 1957, and ulcer symptoms in April, 1958. He was readmitted to the hospital June 14, 1958, 26 months following his operation with massive gastrointestinal bleeding. It was impossible to stablize the patient despite massive transfusions and he died on June 16, 1958.

At autopsy a fistula between the homograft, about 1 cm. distal to the proximal anastomosis, and the proximal jejunum was discovered. There were numerous dense adhesions in the region. Microscopic sections of this region revealed disruption of the wall of the aorta but there were abundant intact elastic fibers adjacent to the fistula.

Comment.—These 2 cases again represent failure of homografts due to inherent technical difficulties in the use of homografts. It is likely that both of these ruptures occurred at the site of the sutured arterial branches of the homograft since the immediately surrounding elastic fibers were abundant and intact. Since the ruptures occurred so late, human error is unlikely and it is supposed that inflammatory and foreign body reaction to the silk suture resulted in eventual necrosis and weakness which permitted dissection of the blood from the homograft into the adherent jejunum.

Thrombosis.—

CASE 7.—A 51-year-old man, with a 1-year history of intermittent claudication, had a femoral arteriogram which showed a short obstruction at the level of the adductor canal with moderately good reconstitution distally. On July 11, 1957, an end-to-side bypass was

performed from the common femoral to the popliteal artery using a frozen homograft. There was return of the posterior tibial pulse. On Jan. 11, 1958, 6 months following operation, the patient noted recurrence of intermittent claudication, and the posterior tibial pulsation disappeared. A femoral arteriogram revealed thrombosis of the graft but there was no evidence of progression of thrombosis in the host vessels (Fig. 5).

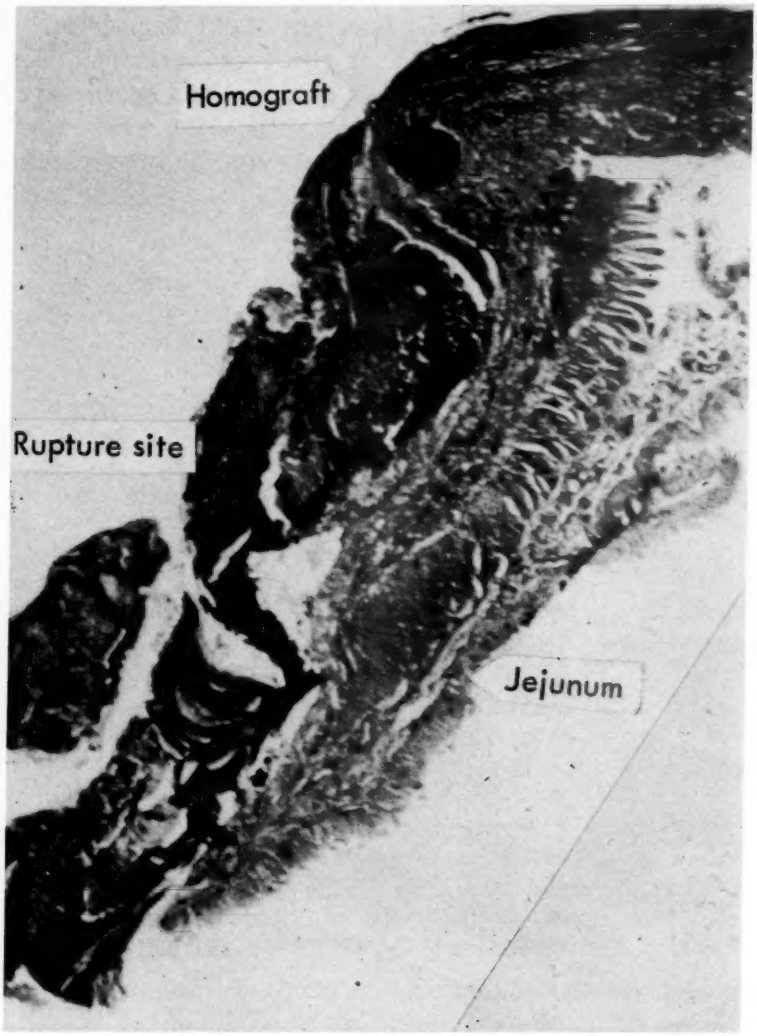

Fig. 4.—Case 5. One edge of the fistula between the aortic homograft and the jejunum is pictured. The graft elastic fibers are abundant and intact to the very edge of the fistula. (Elastic and van Gieson stain ×11.)

Comment.—This case represents failure of a homograft due to late primary thrombosis of the graft, probably related to changes within the graft itself. Arteriograms were obtained on 8 other patients at the time of clinical evidence of late thrombosis in their homografts. In all instances, thrombosis of the host artery at the level of proximal or distal anastomosis as well as thrombosis of the graft was demonstrated. Five of these 8 cases have come to amputation and progression of disease, not primary thrombosis, was futher proved by gross and microscopic study.

Primary thrombosis in the case described resulted in the return of preoperative symptoms which could have been avoided had a more suitable replacement material been used.

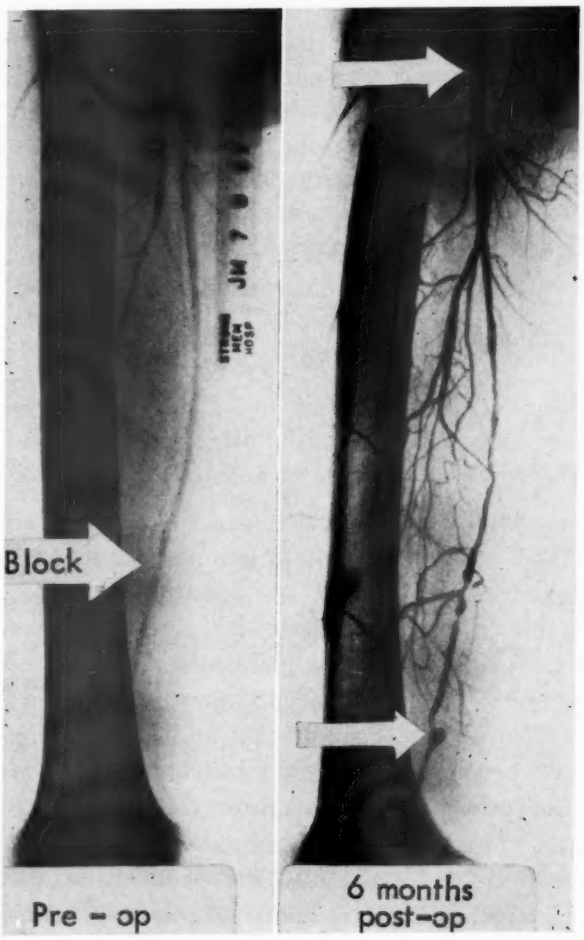

Fig. 5.—Case 7. The site of partial block of the superficial femoral artery was visualized on the preopreative radiograph. The *arrows* on the postoperative radiograph indicated the probable sites of anastomosis of the homograft which had recently thrombosed. Notice the absence of progression of thrombosis in the host artery.

Infection.—

Case 8.—A 73-year-old woman, with a segmental thrombosis of the superficial femoral artery with good reconstitution, had a bypass procedure from the common femoral to the popliteal artery, on April 4, 1958. Five days postoperatively several small pustules were noted on the left lower leg. On the seventh postoperative day the thigh wound was also found to be grossly infected. Bacteriologic cultures from the pustules and from the wound revealed *Staphylococcus aureus* hemolyticus. The patient subsequently developed rupture of the proximal suture line and thrombosis of the graft. She died of septicemia 20 days postoperatively.

A review of the history of the homograft revealed that it had been obtained on Dec. 30, 1957. Cultures of the vessels at that time revealed *B. alcaligenes* and B. proteus. Following sterilization B. proteus was again found. At the time the homograft was used *Staphylococcus aureus* hemolyticus was cultured from the surface of the graft, which was the same organism grown from the wound and from the pustules.

Comment.—This case again represents a failure of a homograft due to inherent technical difficulties in the use of homografts, and in particular the difficulties associated with the sterilization of the grafts.

A homograft which still contains bacteria after sterilization has, in general, been discarded. By error this graft, which was known to contain B. proteus, was used. Although *Staphylococcus aureus* and not proteus was cultured at the time the homograft was used, it seems very possible that the B. proteus overgrew the *Staphylococcus aureus* in the original culture. In fairness to the homograft, it must be said that it was human error that this known infected graft was used. Nonetheless, problems of sterilization are always going to be present with the use of homografts and such errors are likely to recur.

In this instance, the infected homograft resulted in loss of limb and finally loss of life.

PATHOLOGIC CHANGES

The microscopic changes occurring in 13 aortic homografts and 13 femoral homografts for periods up to 26 months after implantation have been studied. The grafts were recovered at the time of autopsy or amputation.

Aortic Grafts.—Particular attention was directed toward the elastic tissue elements (Table III). There were no apparent changes in the elastic tissue of the grafts recovered within 6 months of implantation. At 8 months, one graft revealed thinning due to loss of internal elastic tissue elements but the remaining fibrils were excellent. There was a decrease in thickness of approximately 30 microns. The graft recovered at 15 months (Case 1) showed the most marked changes. The routine hematoxylin and eosin stains of the graft from areas beyond the aneurysm revealed the usual homogenous pattern but, in addition, small cleft-like spaces and poor straining of the media was present. Elastic tissue stains brought out the striking reduction of elastic tissue to only a few strands or isolated swollen fragments. The adventitia was replaced by connective tissue with isolated fibrils. There was an apparent pseudo-intima. On the other hand, 2 grafts obtained at 11 and 26 months were in excellent condition. The elastic tissue was intact and abundant. There was a thick pseudo-intima but no evidence of placquing or other atheromatous changes.

TABLE III. ELASTIC TISSUE CHANGES IN AORTIC HOMOGRAFTS IMPLANTED FOR VARYING PERIODS

TIME IN PATIENT	NUMBER STUDIED	ELASTIC TISSUE (MEDIA)
0-6 months	9	Abundant, intact
8 months	1	Decreased thickness, intact
11 months	1	Abundant, intact
15 months	1	Marked decrease, fragmented
26 months	1	Abundant, intact

Femoral Arterial Grafts.—The femoral arterial homograft sections for study were obtained from amputation specimens and thus represent only portions of the total graft used (Table IV). From these samples it was evident that the graft was treated as an inert substance with exception of those grafts

in which inflammation existed secondary to bacterial contamination. Thrombosis in both the long-term and short-term grafts stimulated acute inflammation and invasion of the graft by polymorphonuclear and mononuclear cells. A 4-month graft containing a thrombus was greatly thinned, having lost the intima and a portion of the media. This partial destruction of the graft may have resulted from reaction at the time of thrombosis. Two long-term grafts revealed splitting and cystic degeneration of the media without evidence of inflammatory reaction. In these grafts the internal elastic tissue was intact. Granulation tissue invaded only at the site of anastomosis in all the grafts. Pseudo-intima is prominent in all the homografts which were in place for 4 months or longer.

It should be pointed out that the two femoral homografts which had become aneurysmal (Cases 2 and 3) did not become available for pathologic study.

TABLE IV. CHANGES IN FEMORAL ARTERIAL HOMOGRAFTS IMPLANTED FOR VARYING PERIODS

TIME IMPLANTED	NUMBER	ELASTIC TISSUE	MEDIA
0-1 month (infected)	3	Necrotic, fragmented One intact	Splitting, inflammation One intact
0-1 month (non-infected)	1	Intact	Focal inflammation
2 months	1	Intact	Intact
4 months	1	Absent	Thinned, focal inflammation
5 months	1	Intact	Intact
8 months	1	Intact	Intact
10 months	1	Intact	Focal degeneration
13 months	1	Intact	Intact
15 months	1	Intact	Focal degeneration; cystic changes
17 months	1	Intact	Focal acute inflammation
24 months	1	Some fragmentation	Thinning and splitting

DISCUSSION

Complications attributable to the use of the homograft as an arterial replacement have been due either to inadequacies of the graft itself or to inherent technical difficulties in the use of homografts which have affected the function of the graft. Inadequacies of the homograft itself have resulted in aneurysmal dilatation, rupture, and thrombosis. Inherent technical difficulties of preservation, sterilization, and suturing of arterial branches on the homograft have resulted in rupture, thrombosis, or infection.

Aneurysm formation has now been reported in 13 homografts (Table II). In addition, Szilagyi[20] has observed dilatation and tortuosity in 12 other femoral homografts. The pathologic changes observed in aneurysmal aortic homografts have consisted mainly in the degeneration of the elastic fibers of the media.[10, 16] This elastic tissue degeneration has been observed within one year of implantation in these reported failures. Similar changes have not been observed in some functioning homografts after longer periods of implantation.[2, 3, 6, 12, 20] The reason for the rapidity of elastic tissue degeneration in certain instances is not known. The pathologic changes noted in aneurysmal or dilated femoral grafts have not been more varied but have also consisted of a sparsity of elastic tissue in some instances, and liquefaction necrosis in others.[20] Again, we have not noted such marked evidence of degeneration in most uncomplicated grafts which

have been implanted for longer periods of time. Unfortunately, we have not been able to predict by pathologic study of the grafts prior to implantation which ones are going to develop such changes. This inability to predict the ultimate fate of the homograft certainly makes their use dangerous.

The free rupture of a homograft has been reported in 15 cases (Table I). With one exception these catastrophes have occurred within 3 weeks of operation. In four instances, pathologic changes were observed in the homograft itself. These changes consisted of fragmentation of the elastic fibers[11] and cystic medial necrosis.[1, 8] In four instances, gross splits in the wall of the graft were observed.[8, 9] The cause of these splits may be related to the inadvertent cracking of the graft when it is in a frozen state.[8] In two instances, the massive bleeding was found to arise at the site of a previously tied arterial branch.[9] These six failures may be due to human error, but they are nonetheless attributable to the use of the homograft since such complications would not occur with a more ideal arterial replacement.

We have observed 2 cases of rupture of homografts into the intestine. In both instances, the rupture was through a small defect which was probably the site of an arterial branch since the surrounding graft appeared intact. Barnes has observed a similar case.[1] Other cases of aorto-enteric fistulas following a homograft replacement of the aorta have been reported,[14] but these have occurred from the proximal suture line, and such complications could follow the use of any type of arterial replacement.

There are 6 reported instances of late thrombosis of femoral homografts which can be attributed to homograft failure and not progression of disease (Table II). In two instances, defects of the graft as the site of a suture were thought to be responsible for the thrombosis.[19, 20] Although two other homografts did not become available for pathologic study, it is assumed that pathologic changes affecting the intima were responsible for the thrombosis in homografts. There are other reported instances of late thrombosis of homografts,[7, 14, 15] but, unfortunately, the arteriographic or pathologic studies did not clearly delineate whether the thrombosis was primary, or secondary to the progression of disease in host vessels. In general, early thrombosis must be considered as probable technical failure and we have not included these as failures of the homograft itself, except for the 2 cases described by Hershey and his co-workers[13] which seem to be true graft failures.

A total of 38 instances of homograft failure are recorded in Table II. The incidence of such failures in large series of cases has ranged from 1.6 to 8.9 per cent (Table V). These complications have occurred during a relatively short experience with arterial homografts. The number will undoubtedly increase with the passage of time and further pathologic degeneration of the homografts.

All of these failures were directly attributable to the use of the homograft as the arterial replacement. The resulting morbidity and mortality was not the fault of the concept of direct surgical attack upon vascular disease but was the fault of the material used. It is our feeling that a synthetic prosthesis is the

TABLE V. INCIDENCES OF FAILURES ATTRIBUTABLE TO THE USE OF HOMOGRAFTS

AUTHOR	FOLLOW-UP	TOTAL HOMOGRAFTS	HOMOGRAFT FAILURES	PER CENT
Szilagyi et al.	Up to 4 yr.	198	8	4.0
Foster et al.	Up to 3½ yr.	122	2	1.6
Humphries et al.	Up to 2 yr.	120	3	2.5
Barnes et al.	Up to 4 yr.	165	3	1.9
Present series	Up to 3½ yr.	90	8	8.9

material of choice for aortic replacements. None of the complications mentioned would have occurred had a synthetic prosthesis been used for replacement of the aortic bifurcation. An autogenous vein is preferred for the replacement or bypass of a peripheral artery.[4, 5] Synthetic prostheses are available, if no suitable saphenous vein is present. A homograft would not be used except in very unusual circumstances and none has been used from our bank since May, 1958.

CONCLUSION

1. Eight complications attributable to the use of homografts as arterial replacements have been presented. The complications have included aneurysmal dilatation, rupture, rupture into the intestine, thrombosis, and infection.

2. Thirty similar cases have been collected from the literature. The incidence of such complications has ranged from 1.6 to 8.9 per cent, in experiences with large numbers of homografts.

3. Microscopic examination of 26 homografts which have been in place for periods up to 26 months has shown elastic tissue degeneration in some of the older specimens which could not be predicted by examination of the original homografts.

4. The morbidity and mortality resulting from these complications would have been avoided by the use of synthetic prostheses for aortic replacements and autogenous veins or synthetic prostheses for peripheral arterial replacements.

We would like to thank Drs. W. J. M. Scott, E. B. Mahoney, W. Southgate, and J. Lyons for permitting us to include their cases in this report.

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ADDENDUM

Since submission of this paper for publication other reports of homograft failures have appeared and the references are listed. They further serve to emphasize the inadequacy of the homograft as an arterial replacement.

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CHANGES IN THE ELASTICITY OF ARTERIAL SUBSTITUTES FOLLOWING IMPLANTATION

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THE morphologic changes in arterial substitutes used to correct aneurysmal and occlusive arterial disease are well known. The associated functional alterations in them, however, have been less clearly defined. This study was undertaken to investigate the elastic properties of different substitutes and to measure the degree and rapidity of the changes in their physical properties associated with their use as arterial grafts.

METHODS

Fresh segments of nine canine aortas and nine equine carotid arteries 7 to 10 cm. in length were refrigerated (5° C.) in Ringer's solution containing penicillin (1,000 units per milliliter) and streptomycin (2 mg. per milliliter). The ages of the donor animals were unknown. Stable volume-pressure curves[5] of these segments and their associated changes in length were determined in a manner previously described[2] with the use of a modified Hallock-Benson apparatus[3] and a vernier caliper. After control data of the arterial test segments were obtained, the canine aortic segments and five of the equine carotid arteries were sterilized (ethylene oxide), lyophilized, and implanted in continuity into the abdominal aortas of dogs. The remaining four equine arterial test segments were partially digested with 0.1 per cent pepsin before being sterilized, lyophilized, and implanted into dogs. The dogs were sacrificed at different intervals and the physical properties of the arterial test segments again measured. Similarly, the stable volume-pressure data of synthetic arterial substitutes were determined both before and at intervals after their sterilization in aqueous Zephiran and implantation. Loose condom rubber sleeves were placed inside the porous prostheses to prevent leaks during testing.

Stable volume-pressure curves were analyzed as follows[1]:

1. The volume distensibility coefficient (D) at a given intraluminal pressure (p) is expressed as percentile change in volume per millimeter of mercury change in pressure, or $Dp = \frac{100 \triangle V}{Vp \triangle p}$ ×

   Vp is the volume at pressure (p),
   v the change in volume in milliliters, and
   p the change in pressure in millimeters of mercury.

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2. The circumferential tension in the wall of the segment at a given intraluminal pressure may be determined as follows:
   $T_c = PR$
   T_c is tangential, arc, or circumferential tension, P the intraluminal pressure in millimeters of mercury, and R the radius in centimeters.
3. Similarly, longitudinal tension developed by the arterial wall at (P) intraluminal pressure is calculated as follows:
   $T_L = \frac{PR}{2}$
   T_L is longitudinal tension, P the intraluminal pressure in millimeters of mercury, and R the radius in centimeters. The assumption that each test segment is a cylinder allows calculation of its radius at any point along the volume-pressure curve ($R^2 = \frac{V}{\pi L}$).

An example of the stable volume-pressure data from a canine aortic segment is plotted in Fig. 1. Only the rising pressure phase of the data has been used to calculate the volume distensibility coefficients and tension-length relationships.

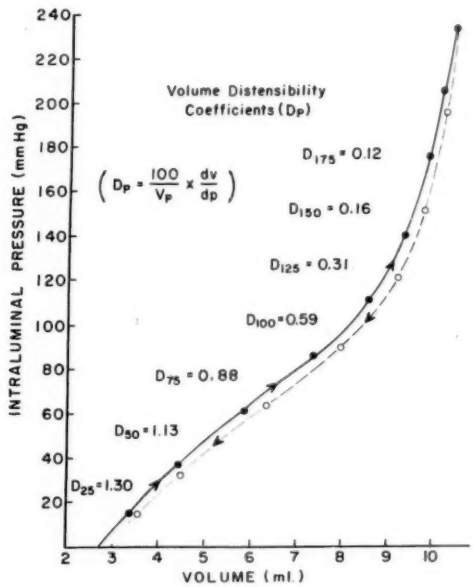

Fig. 1.—A graph of stable volume-pressure data from a canine aorta shows the position of the curve accompanying increases (solid line) and decreases (dotted line) in intraluminal pressure. The volume distensibility coefficients at 25 mm. Hg intervals of intraluminal pressure shown on the left were calculated from the rising phase of the curve.

RESULTS

The data from canine aortas varied with the anatomic segment tested. Differences also were noted in the arteries from similar anatomic sites from both dogs and horses. These may have been related to the age of the donors,[2] but this could not be confirmed because their ages were unknown. The elasticity of canine and equine arteries were measured before and after their sterilization with ethylene oxide, lyophilization, and reconstitution in 0.15 M saline solution

for 20 to 30 minutes. The differences usually noted were: (1) a slightly smaller volume distensibility coefficient at a given intraluminal pressure and (2) a small reduction in the total circumferential lengthening in response to maximal tensions. The latter was 5 to 15 per cent of the control circumferential response. The longitudinal lengthening response was not affected by this procedure.

The Changes in Canine Aorta Elasticity After Homotransplantation.—Soon after implantation, the volume distensibility coefficients and the longitudinal and circumferential responses to tension of canine aortic segments were less than after lyophilization alone. The volume distensibility coefficients were reduced as early as 4 days after implantation. One to 3 months after implantation the volume distensibility coefficients at intraluminal pressures between 75 and 100 mm. Hg were one-half the preimplantation values. After one year, the coefficients had decreased to approximately 10 per cent of the control determinations (Table I, 1a). The greatest changes in elasticity observed occurred within the range of normal blood pressure. The maximum increment in circumference associated with the highest intraluminal pressures used was always less in canine homografts after implantation. The point of sharp increase in the slope of their circumferential tension-length curves usually occurred at lower tensions and after small increments in circumference the longer the period of implantation (Fig. 2).

A comparison of the elastic properties of human iliac arteries after their homotransplantation with the elasticity of iliac arteries from human donors of similar age showed differences similar to those observed in canine aortic segments after homotransplantation (Table I, 1b).

The Changes in Equine Carotid Artery Elasticity After Heterotransplantation.—The reduction in the elastic properties of equine carotid arteries after their implantation in dogs was similar to that following canine aorta homotransplantation. These changes often were slightly greater after the first few weeks of implantation. In two heterografts, the circumferential expansion with rising tension was greater thirteen days after implantation (Fig. 3, *A*), but in both their longitudinal responses to tension and volume distensibility coefficients (above 25 mm. Hg intraluminal pressure) were less after than before implantation (Table I, 2a). The decline in arterial distensibility associated with the implantation of equine heterografts treated by controlled peptic proteolysis was similar to that observed after implantation of untreated equine artery (Table I, 2b).

The Elastic Properties of Synthetic Prostheses.—Woven straight fiber nylon prostheses exhibited less volume distensibility than did the Helanca type of nylon cloth prostheses (Table I, 3a to d). The former tubes had circumferential tension-length curves of small slope at low tensions (0.01 megadynes or less) which abruptly became nearly vertical at higher tensions. The increase in circumference of "nonelastic" nylon tubes was 30 per cent, that of "elastic" nylon tubes 120 per cent at the same high circumferential tension. Dacron tubes woven with spiral "elastic" fibers in the longitudinal axis exhibited only

a 45 per cent increase in circumference when subjected to 0.14 megadyne per centimeter tension and had volume distensibility coefficients which also were less than those of synthetic cloth tubes woven entirely from the Helanca type of thread.

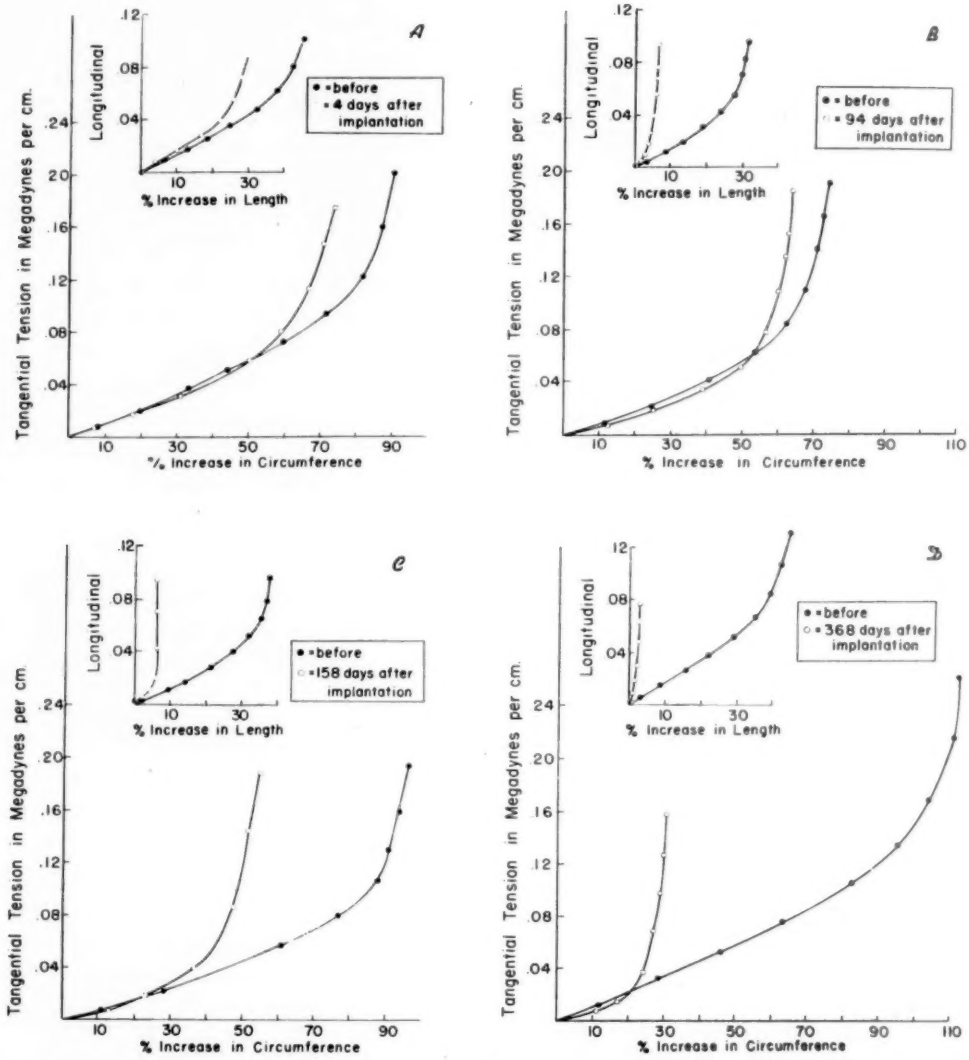

Fig. 2.—The graphs show the circumferential and longitudinal tension-length relationships of canine thoracic aortic segments before and after different periods of homotransplantation (4 to 368 days). The changes in length of the test segments associated with rising longitudinal tension are shown above in each example; the changes in circumference accompanying rising tangential tensions are graphed below.

Changes in the Elastic Properties of Synthetic Arterial Substitutes After Implantation.—Straight fiber nylon prostheses exhibited little change in volume distensibility after implantation if the test segment was studied with the surrounding fibrous sheath in place (Table I, 3a). The increase in circumference in response to circumferential tension was lessened only at lower tensions. When the fibrous tissue sheath was removed from the straight fiber nylon prosthesis, there was a greater circumferential response to increasing tension and larger

volume distensibility coefficients than in the control segments. The straight fiber nylon prostheses did not elongate with increasing longitudinal tension either before or after implantation in host animals. The Helanca "elastic" nylon graft tested one year after implantation still exhibited circumferential and longitudinal responses to tensions although both responses were much reduced.

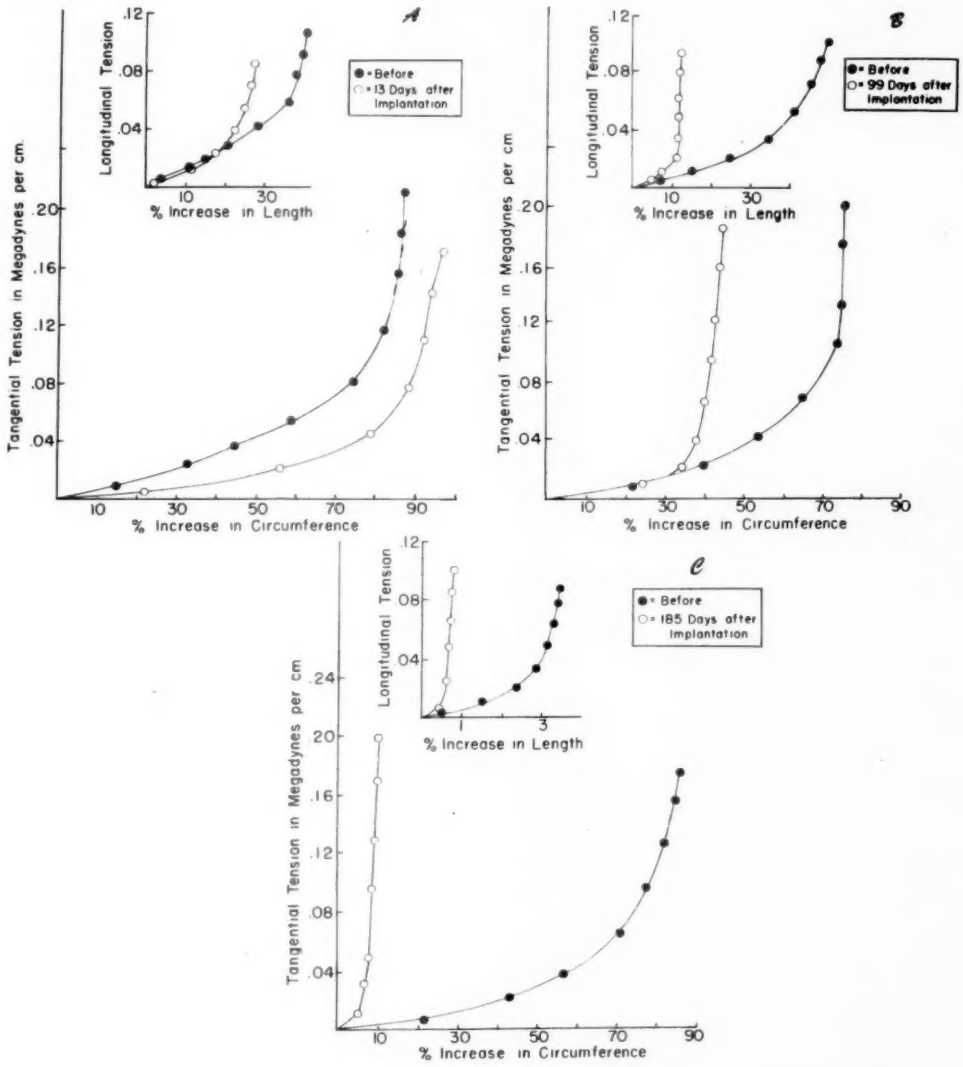

Fig. 3.—The graphs show the circumferential and longitudinal tension-length relationships of three equine carotid arteries before and 13, 99, and 185 days after their heterotransplantation. In each example the longitudinal relationships are graphed above, the circumferential ones below.

A decrease in the circumferential responses to tensions of the Helanca type of Dacron tube had occurred 3 weeks after implantation, although its volume distensibility coefficients were not significantly reduced above 50 mm. Hg intraluminal pressure until the prosthesis had been implanted 27 days (Table I, 3c). The maximum capacity for circumferential and axial elongation was less the longer the Helanca Dacron tube had been implanted (Fig. 4).

Six months after implantation a tension of 0.08 megadyne produced approximately a 25 per cent increase in circumference compared to 90 per cent before implantation. The most notable changes in the slope of the circumferential tension-length curve occurred at lower tensions (0.01 to 0.08 megadyne). The circumference of the control segment increased about 20 per cent between 0.026 and 0.053 megadyne per centimeter tension. However, after 6 months' implantation this tension change produced only 4 per cent increase in the circumference of the scar-encased Helanca type of Dacron tube. The slopes

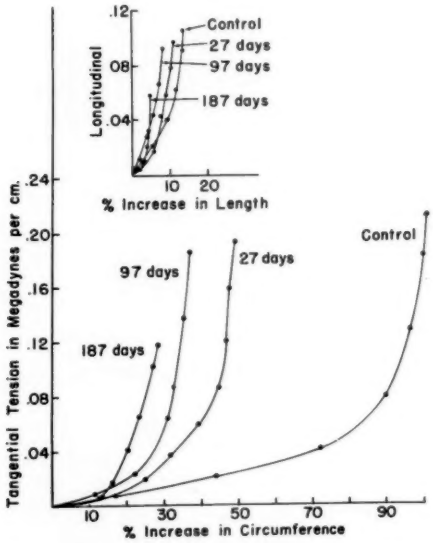

Fig. 4.—The graphs show the longitudinal and circumferential tension-length relationships of a Helanca Fluflon Dacron tube before (control) and after three segments of it were used to replace canine abdominal aortas for periods of 27, 97, and 187 days.

TABLE I. THE VOLUME DISTENSIBILITY COEFFICIENTS OF ARTERIAL SUBSTITUTES AND THE EFFECT OF IMPLANTATION UPON SOME OF THEM
(B-BEFORE, A-AFTER IMPLANTATION)

TYPE OF ARTERIAL SUBSTITUTE		DURATION OF IMPLANTATION (DAYS)	PER CENT CHANGE IN VOLUME PER MM. HG CHANGE IN INTRALUMINAL PRESSURE AT 25 MM. HG	50 MM. HG	75 MM. HG	100 MM. HG	125 MM. HG	150 MM. HG	175 MM. HG
1. Homografts									
a. Canine lower thoracic aortas	1. B		1.07	1.18	1.19	1.16	0.75	0.36	0.20
	A	4	1.06	0.84	0.94	0.62	0.43	0.27	0.19
	2. B		1.01	0.90	0.83	0.71	0.53	0.32	0.18
	A	33	0.89	0.61	0.50	0.31	0.17	0.08	0.08
	3. B		1.30	1.13	0.88	0.59	0.31	0.16	0.12
	A	94	1.17	0.96	0.49	0.25	0.12	0.08	0.07
	4. B		1.05	1.35	1.40	1.76	0.75	0.34	0.19
	A	133	0.79	0.53	0.31	0.23	0.20	0.14	0.09
	5. B		1.33	1.35	1.35	0.94	0.54	0.23	0.14
	A	158	0.98	0.79	0.36	0.18	0.08	0.08	0.07
	6. B		1.24	1.49	1.39	1.35	0.75	0.36	0.17
	A	368	0.69	0.30	0.13	0.10	0.06	0.06	0.06

TABLE I (CONT'D)

TYPE OF ARTERIAL SUBSTITUTE		DURATION OF IMPLANTATION (DAYS)	PER CENT CHANGE IN VOLUME PER MM. HG CHANGE IN INTRALUMINAL PRESSURE AT 25 MM. HG	50 MM. HG	75 MM. HG	100 MM. HG	125 MM. HG	150 MM. HG	175 MM. HG
b. Human iliac arteries	1 Control		1.79	0.85	0.37	0.26	0.19	0.13	0.08
	1. A	14	1.99	0.70	0.20	0.12	0.09	0.07	0.06
	2 and 3 Control		1.40	0.78	0.52	0.38	0.24	0.18	0.15
	2. A	150	1.24	0.57	0.15	0.12	0.08	0.08	0.06
	3. A	340	0.81	0.28	0.10	0.06	0.06	0.06	0.06
2. Heterografts									
a. Equine carotid arteries	1. B		1.62	1.45	1.18	0.61	0.32	0.14	0.07
	A	13	1.90	1.15	0.53	0.27	0.12	0.11	0.07
	2. B		1.88	1.27	0.58	0.34	0.21	0.14	0.10
	A	13	3.13	0.76	0.29	0.20	0.17	0.13	0.10
	3. B		1.80	1.04	0.66	0.36	0.21	0.12	0.06
	A	99	1.00	0.26	0.10	0.05	0.05	0.06	0.03
	4. B		1.71	1.02	0.60	0.37	0.21	0.16	0.13
	A	185	0.15	0.12	0.04	0.04	0.04	0.03	0.03
b. Equine carotid arteries treated with 0.1% pepsin	1. B		1.56	0.79	0.45	0.29	0.16	0.10	0.08
	A	130	0.69	0.32	0.17	0.10	0.07	0.07	0.07
	2. B		1.52	1.01	0.56	0.33	0.18	0.11	0.07
	A	419	0.22	0.08	0.05	0.05	0.04	0.04	0.04
3. Synthetic prosthesis									
a. Straight fiber nylon									
Diameter 7 mm.	B		0.42	0.11	0.10	0.04	0.04	0.04	0.04
1. Scar removed	A	86	0.52	0.23	0.14	0.09	0.09	0.08	0.06
2. Scar removed	A	102	0.31	0.20	0.15	0.11	0.10	0.09	0.07
3. Graft intact	A	213	0.14	0.06	0.06	0.05	0.05	0.05	0.05
b. "Elastic" fiber nylon (Helanca)									
Diameter 7 mm.	B		1.81	1.51	0.75	0.36	0.22	0.17	0.12
Graft intact	A	323	0.20	0.13	0.10	0.07	0.05	0.04	0.04
c. "Elastic" fiber Dacron (Helanca Fluflon)									
Diameter 8 mm.	B		2.23	1.49	0.59	0.27	0.18	0.12	0.09
1.	A	23	1.39	0.82	0.52	0.25	0.18	0.13	0.08
2.	A	27	1.08	0.50	0.31	0.19	0.11	0.08	0.08
3.	A	97	1.07	0.39	0.20	0.12	0.10	0.06	0.06
4.	A	187	0.32	0.19	0.13	0.11	0.10	0.09	0.08
(fibrous sheath from No. 4)		187	0.34	0.21	0.17	0.13	0.11	0.10	0.09
d. Crimped nylon (Edwards-Tapp)									
Diameter 7 mm.			0.60	0.35	0.16	0.12	0.11	0.11	0.11
Diameter 12 mm.			0.30	0.27	0.21	0.16	0.13	0.10	0.08
e. 50% nylon-50% Orlon (straight fiber)									
Diameter 7 mm.			0.34	0.15	0.10	0.09	0.07	0.05	0.05
f. Dacron ("elastic" fiber in longitudinal direction only)									
Diameter 7 mm.			0.67	0.18	0.15	0.11	0.09	0.08	0.08
g. Polyvinyl sponge (12 layers)									
Diameter 7 mm.			0.32	0.18	0.13	0.13	0.14	0.15	0.15
4. Vein autotransplant	A	820	0.51	0.15	0.06	0.03	0.02	0.02	0.02
5. Scar tissue tube*	A	42	0.25	0.14	0.08	0.07	0.06	0.06	0.06

*Formed about a polyethylene rod implanted subcutaneously in a guinea pig.

of the circumferential tension-length curves before and at different intervals after implantation were similar above 0.05 megadyne per centimeter tension. The circumferential tension-length curve of the scar tissue sheath stripped from the Helanca Dacron graft implanted for 6 months was nearly identical with that of the scar-encased intact graft; also, the volume distensibility coefficients of the intact graft were quite similar to those of the fibrous sheath.

The volume distensibility coefficients of the Helanca type of Dacron grafts were progressively smaller the longer the duration of implantation at intraluminal pressures below 100 mm. Hg but were little changed at higher ones (Table I, 3c). The volume distensibility coefficients decreased more rapidly during the first 4 weeks after implantation than they did subsequently.

DISCUSSION

The calculation of volume distensibility coefficients and tension-length relationships used in this study permits the elastic properties of different test segments to be compared quantitatively despite differences in the length and caliber of the segments. The study of cylindrical segments also allows analysis of the responses of test materials to forces similar to those developed in major arteries; it better evaluates the specific directional responses to combined longitudinal and circumferential stresses than does the study of strips of arterial wall.

Employment of these methods has permitted a quantitative study of the elastic properties of common arterial substitutes and the changes produced in them by implantation. Two important findings emerge from these data:

1. Different types of arterial substitutes vary widely in response to stress. Arterial segments to be used as grafts have an elastic behavior similar to that of normal arteries even after their lyophilization and reconstitution in saline solution. Of course, the elastic properties of arterial segments differ with the age of the donor and their original anatomic site. The synthetic prostheses vary, however, from almost rigid pipes (woven straight fiber materials) to prosthetic tubes with responses very similar to those of normal arteries (the Helanca type of synthetic prostheses). A consideration of the responses of arterial substitutes within the range of normal blood pressure would seem most salient. For example, crimped nylon prostheses show acceptable distensibility in lower pressure ranges but very little distention when the intraluminal pressure is increased from 75 to 125 mm. Hg.

2. The elastic behavior of all arterial substitutes after implantation approached that of scar tissue tubes no matter what the preimplantation behavior. The reduction in distensibility appeared to be slightly more rapid in heterografts than in homografts, although the heterografts studied 13 days after implantation had responses to tension greater than before implantation. Synthetic prostheses lost any initial elastic behavior even more rapidly, the process of stiffening being nearly complete one month after implantation. However, none of the various arterial substitutes had significant distensibility over the physiologic range of pressures after having been implanted for from 3 to 6 months.

The observation that all types of prostheses have similar coefficients of distensibility after sufficiently long implantation suggests that scar tissue is a principal determinant of these final elastic moduli. Five observations support this hypothesis: (1) The greatest reductions in elasticity of all types of arterial substitutes occurred during the first month after their implantation—the time during which most of the scar tissue was deposited. (2) The elastic properties of the scar tissue sheath surrounding one Dacron prosthesis were the same as those of the intact graft. (3) The response of a scar tissue tube formed about a polyethylene tube in the subcutaneous tissue of a guinea pig was quite similar to those of the long-implanted arterial substitutes (Table I, 5). (4) Although the straight fiber nylon grafts differed little from their controls, removal of the adherent scar from about them resulted in volume distensibility coefficients and circumference lengthening responses which exceeded the control values. In other words, the surrounding scar tissue of the intact graft prevented the increased responses attributable to weakening of the long-implanted nylon material.[4] (5) The near-vertical parts of the tension-length curves of long-implanted arterial substitutes appear as acute inflections at low tensions. The scar tissue deposited about the test prosthesis and its contracture probably are responsible for the onset of this "collagenous" phase of the curve at such low tensions.

These findings suggest that any physiologic advantage of "elastic" arterial prostheses must be limited to the immediate postoperative period.

SUMMARY

The elastic properties of various arterial prostheses were investigated quantitatively before and after their use as arterial grafts. The elastic behavior of different arterial substitutes varied widely. Of the synthetic prostheses studied, only the cloth tubes of the Helanca type had physical properties similar to those of normal arteries. All "elastic" arterial substitutes tested—homografts, heterografts, and the Helanca type of synthetic tubes—soon stiffened after implantation. Synthetic prostheses appeared to stiffen more rapidly after implantation than did the arterial segments tested, though the process in the latter was virtually complete in 6 months. The volume distensibility coefficients and tension-length responses of both implanted synthetic tubes and arterial segments declined to near those of scar tissue tubes. Evidence is presented to support the concept that these reductions are caused by the scar tissue which is deposited about the implanted arterial substitutes.

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VENOUS THROMBOEMBOLISM

A Summary of 10 Years' Experience With 610 Patients and the Evolution of a Routine Management

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THIS report will present observations that provide practical answers to the questions of management that usually arise with venous thromboembolism. The problem of what to do when venous thromboembolism is only suspected can be very disquieting for both patient and physician. And when a course of treatment is decided upon in the suspected or obvious case, the decision to stop therapy is often made with uncertainty. These problems arise because the usual clinical guides are not always reliable. It is generally known that the three important, interacting factors to consider in thromboembolism are Virchow's triad of vascular damage, slowing of the blood flow, and unknown abnormalities in blood composition. It was presumed that, if these three factors could be appraised in each patient, a better control of this thromboembolic problem might be achieved.

The amount of vascular damage and stasis can be clinically estimated for practical purposes, but an easy, reliable index of the blood abnormalities remained elusive. Proceeding on the belief that studies of total physicochemical blood changes might provide an adequate answer, a simple, bedside drop test for blood to reflect these changes was devised and applied.[7] The experiences gained with the use of this test on 610 patients with known or suspected venous thromboembolism during the past 10 years indicate that its results considered in relation to venous damage and blood flow are trustworthy guides to lead a maximum of such patients safely to recovery with a minimum of treatment and loss of time.

METHODS

The Blood Drop Test.—The details of this test have been fully described in a previous report.[7] Essentially, it consists in timing, under standard conditions of temperature and pressure, the interval taken by 14 drops to fall away from the tip of a standardized and sterilized test instrument containing 1 ml. of blood drawn directly into it from a vein. This drop measuring instrument (stactometer) is made up of a 1 ml. tuberculin-type syringe barrel with a 25 gauge, ½ inch hypodermic needle attached. The blood drop time thus obtained is divided by the water drop time standard which has been previously

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established for each stactometer by timing its delivery of 14 drops from 1 ml. of 25° C. distilled water. The result is called the stactometric ratio (hereafter referred to as SR) and represents in one figure the combined effects of viscosity, surface tension, and specific gravity which are reflections of the physicochemical state of the blood. Since the rate of blood dropping from the stactometer is grossly dependent on the combined effects of the cellular and plasma elements, a hematocrit determination was performed on the same sample of blood to help explain some of the SR fluctuations due to anemia, polycythemia, hemoconcentration, or leukemia. The test drops and the remainder of the milliliter of blood were caught in a heparinized test tube and used to provide the hematocrit figure. Plasma protein variations, particularly the globulin and fibrinogen fractions, also influence the SR, but their consideration is not necessary for present practical purposes.* The SR and hematocrit of each subject were recorded on an individual graph in which the horizontal axis shows the date of each test while the vertical axis indicates

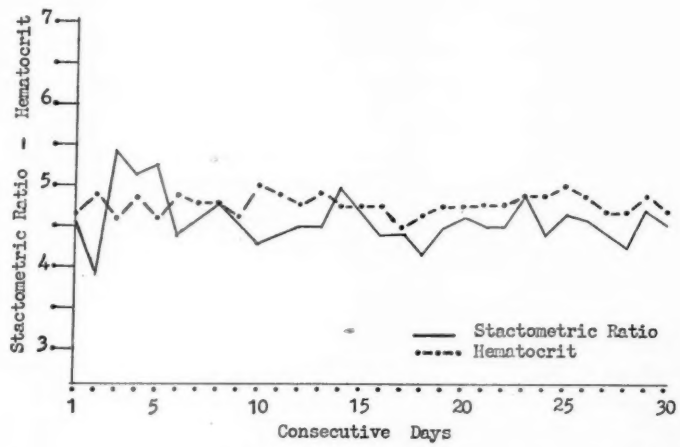

Fig. 1.—A copy of 30 consecutive daily stactometric ratio and hematocrit test results on a 38-year-old normal man. The elevation of the stactometric ratio on days 3, 4, and 5 was during an upper respiratory infection.

the SR and hematocrit (Fig. 1). It was found that the SR line was consistently below the hematocrit line when the subject was in a state of well-being and rose above the hematocrit line when he was under mental or physical stress. This empirical relationship between the SR and hematocrit figures made the hematocrit a convenient base line along which SR fluctuations could be plotted in terms of plus or minus variations according to the following formula: SRV = 10SR – H, in which SRV is the stactometric ratio variation, SR the stactometric ratio, and H the hematocrit in per cent. Thus, 3 SR of 4.0, 4.5, and 5.0 each with a hematocrit of 45 per cent would have stactometric ratio variations (hereafter referred to as SRV) of –5, 0, and +5, respectively. The condition of clinical well-being is associated with minus SRV (average of –5 in females and –2 in males) while plus SRV indicate a

*The protein phase of the research was aided by a grant from the Washington Heart Association.

disturbance in this normal blood phsicochemical balance. (This altered physicochemical state of the blood can be present or absent independently of such systemic reaction indicators as fever or increased sedimentation rate.) The intensity of this disturbance apparently depends upon the severity of the offending stimuli and the capacity of the individual's mechanisms to react. The effects of these reactions on the SRV may vary from day to day. In order to classify a patient's SRV repsonse type and provide a figure on which to base prognosis, the technique of determining the mean variation over a period of days was used. It was found that a 5-day average was, with very few exceptions, adequate. This average SRV (hereafter referred to as ASRV) was calculated from the algebraic sum of 5 consecutive daily SRV (the results in this report are based on consecutive, single, daily tests), that is, 5 consecutive daily SRV of +2, –1, +4, +3, and –2 add up to +6 which divided by 5 gives an ASRV of +1. The average of 0 was included with the minus results and these made up the minus ASRV group while the plus readings were labeled the plus ASRV group. Adapting this to venous thromboembolism, it was decided that treatment of such patients should continue until the SRV average on the minus side (Fig. 2).

I have performed this blood drop test over 20,000 times on more than 1,800 subjects during the past 10 years.

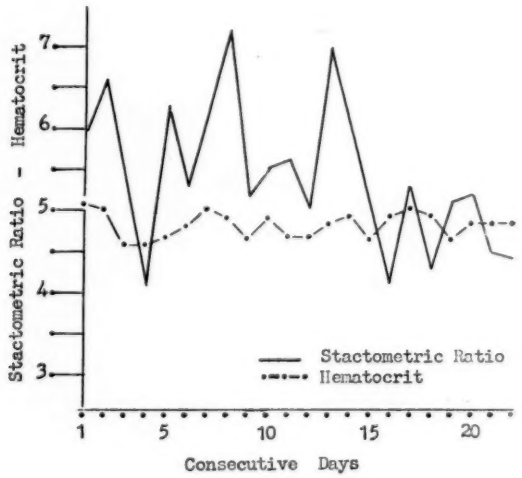

Fig. 2.—A copy of the stactometric ratio and hematocrit record on a 34-year-old man with a fracture of the right femur which had been treated by open reduction on the day before this record was started. He had bilateral calf tenderness, right lower extremity edema, pleuritic chest pain, and dyspnea. The initial ASRV was +8 and the last ASRV was 0. He was treated with heparin and made a good recovery.

PATIENTS

The 610 patients in this study all had a presumptive diagnosis of venous thrombosis, pulmonary embolism, or both, made by referring physicians. However, despite the signs and symptoms generally recommended as guides in the early recognition of these conditions, a definite diagnosis could not always be made from clinical findings even by one who encounters these problems frequently. While the diagnosis was usually quite obvious, it was not certain

in about a third of the patients seen. In order to provide a clearer definition of the patient types, a few simple criteria were set up for a definite diagnosis and the patients grouped as they presented in familiar clinical patterns. They were subdivided as follows:

1. *Superficial Venous Thrombosis.*—The involvement of an obvious superficial vein in inflammation as evidenced by pain, redness, and a tender, cordlike induration in and along its course, without edema of the affected extremity, was manifested.

2. *Deep Venous Thrombosis.*—The occlusion of the iliac, femoral, popliteal, tibial, axillary, or brachial veins, or combinations of them was seen, as indicated by overlying pain and tenderness with recent, obvious edema, and prominence of the superficial veins distal to the point of occlusion.

3. *Superficial and Deep Venous Thrombosis.*—A combination of the features of Groups 1 and 2 were demonstrated.

4. *Pulmonary Embolism With or Without Infarction, Source Unknown.*—Pleuritic chest pain or sudden shock and dyspnea associated with hemoptysis, x-ray evidence of an abnormal pulmonary shadow or electrocardiogram indication of acute cor pulmonale without peripheral evidence of venous thrombosis, gave evidence of this group.

5. *Suspected Venous Thromboembolism.*—Patients who had pain and tenderness over the course of the major veins in an extremity or sudden pleuritic chest pain or both without the more confirmatory signs set forth in Groups 1, 2, 3, or 4, constituted this group. Homan's sign was present in 20 per cent of the 163 patients having leg signs and symptoms. There may be edema that is less than can be seen with the naked eye or the obvious edema of probably exclusive lymphatic obstruction which appears as a doughy, usually unilateral, and slowly progressive swelling without dilatation of the superficial veins.

Sixty of the 610 patients had only 1 or 2 consecutive tests but for various reasons could not be followed with further serial SRV determinations. As was pointed out in a previous report,[7] 1 or 2 tests with minus results are not always a reliable guide for prognosis because of the drop in SRV for a day or two after a thrombosis or embolism. These inadequately tested patients will not be included in the main analysis, but the outcome reports that were available on most of them did help provide some clarifying points which will be mentioned later.

The 550 patients who are the substance of this report are grouped with their pertinent characteristics in Table I. The prominent base line features usually emphasized by other analysis of venous thromboembolism groups are: Sex, 290 males and 260 females. Age, from 19 to 92 years with the mean age at 52 years; 79 per cent were over 40 years old. Predisposing conditions, 532, included surgery in 20.9 per cent, fracture and trauma in 16.6 per cent, postpartum in 2.5 per cent (these 3 predisposing conditions are labeled "traumatic" while the rest are labeled "nontraumatic" in Table I), past history of venous thrombosis in 18.8 per cent, varicose veins in 15 per cent, cancer in

TABLE I. PERTINENT DATA ON 550 PATIENTS HAVING A PRESUMPTIVE DIAGNOSIS OF VENOUS THROMBOSIS

PERTINENT CHARACTERISTICS	CLINICAL TYPES					ASRV OF CHARACTERISTICS		TOTAL
	VENOUS THROMBOSIS			EMBOLISM (SOURCE UNKNOWN)	SUSPECTED VENOUS THROMBOEMBOLISM	PLUS	MINUS	
	DEEP	SUPERFICIAL	SUPERFICIAL AND DEEP					
Patients	192	104	34	23	197	226	324	550
Male	111	40	20	19	100	138	152	290
Female	81	64	14	4	97	84	176	260
Mean age	53	52	55	46	52			
Predisposing conditions	154	89	31	20	137	186	245	431
Traumatic	102	23	15	6	76	112	110	222
Nontraumatic	52	66	16	14	61	74	135	209
None	38	15	3	3	60	36	83	119
Embolism	61	5	7	23	None	58	38	96
Single	53	5	6	16	None	44	36	80
Multiple	8	None	1	7	None	14	2	16
Treatment (average days)	14	7	23	13	8	15	7	11
Specific*	163	33	24	20	33	189	84	273
Nonspecific	29	71	10	3	164	73	194	277
Plus ASRV	100	21	19	18	68	226	None	226
Minus ASRV	92	83	15	5	129	None	324	324
Results								
Thrombosis	20	21	14	1	2	37	21	58
Embolism	24	None	9	4	3	30	10	40
Fatal	6	None	None	4	3	10	3	13

*Anticoagulant therapy or vein ligation.

10 per cent, cardiovascular disease in 9.2 per cent, and miscellaneous (polycythemia, leukemia, infection, and obesity) in 4.4 per cent. These conditions were distributed among 431 patients (78.3 per cent) and 101 patients (23.4 per cent) had 2 or more predisposing conditions. In 119 patients (21.6 per cent) the venous thrombosis was apparently spontaneous. Ninety-six (17.4 per cent) had at least one pulmonary embolism with their present illness when they came under observation. Extremity involved was the lower in 98.9 per cent, the left in 49.6 per cent, the right in 34.7 per cent, and both in 14.6 per cent. Other points of possible interest not included in Table I are that there was a 3 per cent increase in incidence of venous thrombosis in the spring and a 7 per cent increase in the fall and the average duration of illness before consultation was requested was 6 days.

GENERAL CONSIDERATIONS

The present routine of management of a known or suspected case of venous thromboembolism evolved over a period of 6 years and 265 adequately observed patients. SRV on these patients were merely recorded for future reference and did not influence treatment which was guided by the usual clinical signs, symptoms, and systemic reactions. The experiences and ensuing reflections

that resulted in this method of management included scrutiny of causes of venous damage, blood physicochemical changes as indicated by SRV, stasis of blood flow, embolism, and the reasons for failures of treatment.

Venous Damage.—Venous thrombosis starts from damage to the endothelial lining of the vein. This damage can be locally inflicted by physical or chemical agents inside or outside the vein or be the result of inflammation within the vein walls from causes that are not apparent. The important thing to determine is the cause of the venous damage and whether or not it is still operating. Generally, a knowledge of the type of surgery or trauma about the involved vein, the presence there of infection, abscess formation or tumor (particularly cancer whether nearby or distant), the type and frequency of intravenous injections, and the extent of venous thrombosis will provide some useful answers to causes of many venous thromboses. However, the cause of the thrombosis often will have ceased to operate when the patient is first seen. The continuing assault of a cause is usually seen in local infections, cancer, extensive intravenous clotting, and in vein wall inflammation of unknown cause.

Extensive intravenous clotting compounds the problem because a thrombus stimulates inflammation in the vein wall which causes further endothelial damage. This cycle occurring over a wide area makes treatment difficult, particularly when the factor of stasis is added. Failure of seemingly adequate anticoagulant therapy was due partly or wholly to this problem in 5 patients.

Inflammation of the vein wall without apparent direct cause occurred in 58.6 per cent of the 353 patients with obvious venous thrombosis. It seemed to occur in those who had varicose veins, a past history of venous thrombosis, cardiovascular disease, gout, diabetes, obesity, leukemia, polycythemia, cancer, and thromboangiitis obliterans; in 16.7 per cent of the 353 patients there was no associated or predisposing condition at all. The venous thrombosis was usually in the superficial veins but not infrequently involved the deep veins. Most of these patients seemed to share a number of clinical characteristics. Many had been through one or more attacks of venous thrombosis, often in the same vein, and frequently gave a past history of bursitis, tenosynovitis, arthritis, ruptured intervertebral disc, "weak joints," generalized "painful muscles," gross muscle fiber tears (particularly the gastrocnemius or plantaris muscles), easy bruisibility, and a strong allergic history. This frequently recurring background, the abundance of connective tissue in vein walls, the flare-up of venous thrombosis during an emotional or physical stress, and the usually very low (–5 or less) ASRV in these patients suggests that, in a considerable number, the venous damage and thrombosis is a manifestation of a basic connective tissue problem with one of the target systems being the veins. This finds some further confirmation in the reports that many venous thromboses respond well to anti-inflammatory drugs.[5, 8]

The association of cancer is mentioned in most discussions dealing with venous thrombosis, but the nature of this relationship is still uncertain. In this series there were 57 patients (10 per cent) with cancer. In 17 of the

57 patients (29.8 per cent), the venous thrombosis preceded the diagnosis of cancer sometimes by several months. Forty-five (78.9 per cent) of the malignancies were in the pelvic region (colon 20, prostate 11, cervix 4, ovary 3, uterus 3, rectum 3, and bladder 1), while the rest were distributed elsewhere (breast 3, lung 3, pancreas 2, and 1 each in the spine, stomach, nose, and liver). The fact that 78.9 per cent of the malignancies were in the pelvic region along with lower extremity thrombosis suggests that some of the thrombosis may be due to local venous damage caused by the reactions of encroachment by the cancer. On the other hand, the occurrence of venous thrombosis in veins distant from the cancer, the appearance of the venous thrombosis in some cases months before the cancer is diagnosed, the resistance of the venous thrombosis to treatment until the cancer is removed, and the return of the venous thrombosis with the recurrence of the cancer, and the 70.9 per cent incidence of low minus ASRV in cancer–venous thrombosis patients indicate that the cancer may be associated with systemic effects that cause thrombosis in patients prone to venous disease. These cancer–venous thrombosis relationships have also been reported by Durham.[4]

In summary, endothelial damage can be caused by a variety of factors that can usually be determined through a history and physical examination. If these factors are still operating and subject to control, they should be suppressed. If they cannot be controlled, the clotting mechanism should, then, be curtailed until is is determined that no blood thrombotic state is occurring and the factor of stasis is eliminated.

Blood Physicochemical Variations as Reflected by SRV.—The application of blood physicochemical variations in venous thromboembolism was developed by correlating the various clinical findings, courses, and treatments with concurrent SRV patterns.

The main body of patients confirmed the previously reported impression that plus ASRV forebode more trouble while minus ASRV pointed to uneventful recovery. The few exceptions to this general rule were provided by special small groups of patients who happened to be in the necessary combination of circumstances to clarify the picture.

The SRV preceding the clinical appearance of venous thrombosis or embolism was demonstrated by 11 of 128[7] postoperative patients who were selected for study because they were, by clinical evaluation, likely candidates for venous thromboembolism. All 11 had an ASRV of +7 or more *before* these complications were diagnosed but only 5 continued to have such high ASRV afterward. Thus, it seems that the initial clinical venous thrombosis is preceded by high plus ASRV and this "thrombotic" SRV state may or may not persist or recur. When it did persist or recur there was likely to be more thrombosis or embolism (Fig. 3).

Additional information was provided by 10 patients on whom long-term follow-up was possible. These patients were part of a group selected for prolonged study aimed at shedding more light on the relation of stress, SRV, and thrombosis. They had either a past history of two or more episodes of venous thrombosis or unusually high (+10 or more) original ASRV or both,

and have been under observation from 1 to 10 years. Their SRV were determined about once a week. Thus, they were tested under the stresses and strains of work and personal life, major and minor illnesses, surgery, seasons of the year, and the process of aging. The SRV patterns were found to vary between two extremes. On the one hand, were 4 subjects whose SRV have been essentially normal since their original high ASRV except for occasional low plus readings when they were under unusual mental or physical stress or during the wide temperature excursions of spring and fall. None of these 4 patients has had any further venous thrombosis. At the other extreme was a 36-year-old man who has been observed for over 5 years and has had only 93 sporadic normal readings in a total of 527 tests. During the course of the first 9 months of observation, this patient had both femoral veins and finally the inferior vena cava ligated because of numerous pulmonary emboli which could not be controlled with anticoagulants, and he has continued to have recurrent attacks of venous thrombosis every few months since. The other 5 patients showed varying patterns of persistence and recurrence of high plus SRV and all have had at least one episode of venous thrombosis (a total of 37) subsequent to the one that brought them into the study. Here again the venous thrombosis usually occurred during a plus SRV period and its severity and duration paralleled the plus SRV persistence (one simmered on for 6 months).

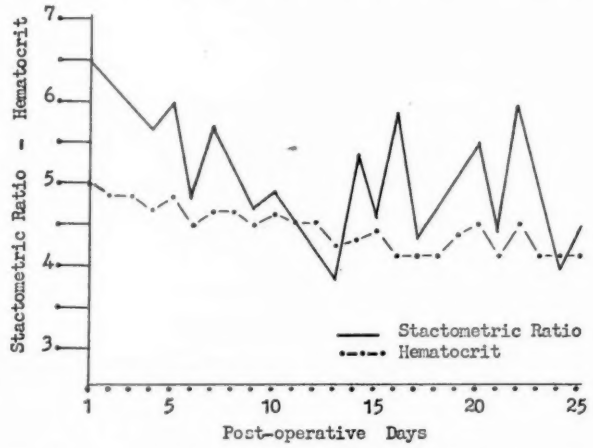

Fig. 3.—A copy of the stactometric ratio and hematocrit record on a 72-year-old man who had undergone a colon resection for carcinoma. He developed pain in the left calf on the tenth day and edema of that leg on the fourteenth day. A left femoral vein exploration and ligation on the fifteenth day confirmed the diagnosis of venous thrombosis. He developed a pulmonary embolism on the seventeenth day and was placed on heparin therapy. He progressed quite well until the twenty-fourth day when he had another pulmonary embolism and suddenly died on the twenty-fifth postoperative day. The postoperative, 5-day ASRV was +12 and the ASRV for the 5 days preceding death was +5.

On 3 occasions, a localized area of superficial venous thrombosis occurred in the absence of plus SRV but the process subsided in a few days without treatment. These 10 patients and 24 others not followed regularly, but seen during episodes of recurrent venous thrombosis during the past 10 years, and 68 others giving a past history of venous thrombosis suggest that some individuals are prone to venous disease which can flare up because of local or general conditions. But once started, the severity and duration is usually

dependent upon the persistence of the general condition that is reflected by plus SRV. The exception to this is when the extent of thrombosis occurring during the thrombotic state is sufficient to sustain recurrent thromboembolism on the basis of continued operation of causes for venous damage or stasis. In this latter type of situation, the SRV may be on the minus side for more than 5 days, but the extensive thrombosis will be clinically obvious and has been seen in patients whose present thromboembolic illness has been going on for 3 weeks or more. Such patients should have their SRV observed daily for at least 2 and preferably 3 weeks under ambulatory conditions before treatment is stopped. However, in 95 per cent of the patients, the 5-day ASRV is adequate to indicate a trend for a known or suspected case of venous thromboembolism.

The usual treatments for venous thromboembolism do not have any readily apparent effect on plus SRV. The 2 conditions in which plus SRV can be quickly corrected is in polycythemia by therapeutic bleeding and in hemoconcentration by hydration. Two other situations usually associated with high plus SRV in which the blood may be influenced toward normal in a few days are the drainage of an abscess and the closure of a biliary fistula.

In summary, plus SRV seem to reflect a thrombotic state of the blood during which thrombosis may occur if there is concomitant vascular damage. This thrombotic state may be temporary and not recur or may persist for years. (This concept has been also suggested by Allen[1] and Wessler.[10]) In between are varying patterns of persistence and recurrence. Unless the cause of the elevated SRV can be controlled, treatment should be directed at curtailing the clotting mechanism during periods of SRV elevations.

Stasis.—Slowing of the normal blood flow encourages the propagation of an existing thrombus. The degree of slowing necessary to do this depends on blood and cardiovascular factors that may vary from patient to patient. However, since there is likely to be some degree of stasis until a patient is fully ambulatory, the blood flow is not considered good until the patient is up and about in a normal manner.

Embolism.—The breaking or complete dislodgment of a thrombus depends upon the accidental concomitance of several conditions. Essentially, embolism may be expected to occur when certain forces induced by movement act upon a nonfixed, friable thrombus. There are many factors involved in clot fixation which is probably dependent upon clot retraction which in turn is influenced by several blood constituents as indicated by Quick.[6] Abnormalities in these processes lead to varying degrees and durations of clot friability. Thus, the prevailing conditions for embolism at any given time cannot be evaluated and until it is fairly certain that no further thrombosis has taken place, the chance of clinically manifested embolization can be expected in about 25 to 30 per cent of deep venous thromboses. In fact, embolization probably occurs much more often without alarming clinical signs as indicated by Towbin[9] who quotes Ceelen as stating: "In very careful dissections of the arteries

of the lung, in cases where there are thromboses on other parts of the body, there will be found emboli in the lungs in 75 per cent of cases.'' This embolic probability may be reduced by curtailing the activity of a patient with venous thrombosis or embolism to bathroom privileges for at least 48 hours during which any formed thrombi will ordinarily become fixed and new thrombosis minimized by anticoagulant therapy.

Reasons for Treatment Failures.—The analysis of the thromboembolic complications and fatalities in the first 265 adequately observed patients brought out five main reasons for treatment failures.

1. *Inadequacy of clinical guides:* These were situations in which the usual clinical guides (pain, tenderness, activity, and systemic reactions) were not sufficient to indicate the type or duration of treatment thus resulting in inadequate therapy. Here were 16 episodes of thrombosis, 16 of embolism, 5 of which were fatal. The ASRV of the fatalities were +5, +9, +10, +11, and +15, respectively.

2. *Contraindications to specific treatment:* Included here were patients whose source of emboli was uncertain and who also had active or probable bleeding sites or persistent hypoprothrombinemia. There were 2 instances of thrombosis and 3 of embolism, 2 of which were fatal. The ASRV of the fatalities were +8 and +15.

3. *Terminal states:* Here were patients who were in the irreversible, final phases of chronic cardiovascular disease, or long-standing, untreated thromboembolism. The patient was usually aged, very ill, and bedfast with congestive heart failure or extensive pulmonary damage (as with 2 patients who had multiple pulmonary abscesses from recurrent pulmonary embolism) which created an intractable stasis problem that was often complicated by renal and hepatic damage which made anticoagulant therapy very difficult. The source of emboli in these patients was usually from mural thrombi which are not readily controlled by anticoagulant therapy. Here were one episode of thrombosis and 3 of fatal embolism. The ASRV of the fatalities were –1, –2, and +2, respectively.

4. *Treatment control lag:* The period between the initiation of treatment and effective control of the disease process and the existence of embolic sources from recently formed nonorganized thrombi results in a lag period of about 3 days after the beginning of management during which emboli or extension of thrombosis may occur. Four thromboses and 3 emboli occurred during this interval. There was one fatality occurring on the first day of observation and is not included in Table I or II because a 5-day ASRV was not possible; this patient's SRV was –3.

5. *Obscure causes of vein wall inflammation:* Included here are the complications occurring in superficial venous thrombosis, in those with long-standing thromboembolism (3 weeks or more) and in cancer-venous thrombosis patients. There were 20 episodes of thrombosis and 4 emboli without any thromboembolic

fatalities in this subgroup. Eleven of the thromboses were in superficial venous thrombosis patients and 6 other thromboses and 2 of the emboli were in cancer patients. Neither the clinical signs nor the 5-day ASRV were adequate guides to forecast further thromboembolic complications in this type of patients; however, it does suggest that a patient having recurrent venous thrombosis with minus SRV should be observed for possible cancer.

ROUTINE OF MANAGEMENT

The general plan was to estimate the relative active role of venous damage, blood SRV, and stasis in each patient so that treatment may be adapted to fit the particular situation. The following basic rules were formulated to meet the usual contingencies that arise in the treatment of venous thromboembolism.

1. Patients having any form of obvious deep venous thrombosis or pulmonary embolism and all patients having plus SRV will be given anticoagulant therapy until they are normally ambulatory and their SRV average minus over a period of: (a) 5 days in the usual patient, or (b) 15 days in patients whose duration of present thromboembolic illness is over 20 days.

2. Patients having recurrent (3 or more) pulmonary emboli despite adequate anticoagulant therapy will have a deep venous ligation above the area of thrombosis.

3. Patients having minus SRV and obvious superficial venous thrombosis or suspected venous thromboembolism may be given symptomatic, anti-inflammatory or other treatments, depending on modifying circumstances.

General Measures.—The routine started with an evaluation of each patient through a history and physical examination directed at determining the location of the involved veins and possible local or general causes for venous thrombosis which could be treated. The local causes looked for have been mentioned under venous damage. General conditions that stood out as aggravating and perhaps helping cause venous thrombosis included polycythemia and hemoconcentration which markedly alter the physical state of the blood, cardiovascular disease, particularly when complicated with congestive heart failure, sustained emotional stress, and the hypersensitivity diathesis. When local or general causes were found they were treated with the usual methods. Bed rest was ordered for those with recent pulmonary embolism or excessive edema or pain in the affected extremity which was comfortably elevated. Ambulation was encouraged as soon as it could be undertaken with relative comfort; analgesics helped hasten this. Elastic bandages or stockings were used to control the edema and discomfort when the patient became active. Daily SRV determinations were made on the patients while they were in the hospital, and follow-up tests were obtained at weekly or more frequent intervals until the patient resumed normal life. Progress reports for at least 2 months were obtained on all the adequately tested 550 patients.

Anticoagulant therapy: This centered about the use of heparin while Dicumarol was given only in the relatively few situations in which it was indicated.

1. Heparin. This was the anticoagulant of choice because of its immediate anticoagulant effect and its relative safety. The only absolute contraindications considered were an active bleeding site or a history of a known concealed bleeding site in the brain, spinal cord, or abdomen. The routine followed was to give 100 mg. concentrated (100 or 200 mg. per milliliter) aqueous heparin intramuscularly in the gluteal region every 8 hours in the average-sized individual (every 6 hours in patients over 180 pounds and 75 mg. every 8 hours in those less than 110 pounds). A venous clotting time (Lee-White) was obtained at least once during the course, the first usually before the fourth dose to make certain that the heparin effect was not accumulating. There were only 5 patients of the 278 (1.8 per cent) given heparin who developed complications necessitating its discontinuance; 4 had a gross hematuria and the other had an allergic reaction. Bauer[2] reported on the use of heparin (300 to 400 mg. intravenously a day) in 627 cases of venous thromboembolism over a period of 13 years without serious hemorrhage and without clotting time determinations for control. Discontinuance of routine heparin therapy was done gradually over a period of 2 to 3 days.

2. Dicumarol. This drug was used in the relatively few patients (10.2 per cent) who required anticoagulant therapy for more than 2 weeks. Those needing prolonged treatment usually showed initial SRV of +10 or more and Dicumarol was started during the first few days of observation concomitantly with heparin. The usual schedule was 300 mg. Dicumarol the first day, 200 mg. the second day, and 100 mg. the third day. Dosage was guided by daily determination of the prothrombin time (Quick, one stage) which was prolonged to about 2½ times normal when heparin was stopped and a maintenance dose of Dicumarol established. When Dicumarol therapy was no longer needed, the dose was tapered off over 4 to 5 days. Two serious complications occurred with Dicumarol, one a hemiplegia with recovery and the other a serious hemorrhage into the calf muscles resulting in prolonged disability.

Venous ligation: Since the start of this study in 1948, deep venous ligations became progressively fewer and none have been necessary on the last 200 patients. Twenty femoral vein and 3 inferior vena cava ligations have been performed in the total series. Long saphenous vein ligations were performed on 21 patients who had superficial venous thrombosis in varicose veins.

Anti-inflammatory therapy: It became apparent early in this search that a considerable number of venous thromboses were due to inflammation in the vein wall without a known cause. These were usually associated with minus ASRV and found particularly in the superficial veins and not infrequently in the deep veins. Attempts to control this inflammation were made

with the use of intramuscular trypsin, 1 ml. (5 mg.) every 8 hours for 5 days as modified from Innerfield[5] or phenylbutazone (Butazolidin), 200 mg. three times daily for 3 days then 100 mg. three times daily for another 4 days as recommended by Stein.[8]

These treatments were usually used singly, but sometimes combinations were tried, particularly ligation and anticoagulant therapy or anticoagulant therapy and anti-inflammatory therapy, with uncertain effects on the results.

RESULTS

The results of this routine of management in 285 patients over the past 4 years are recorded as Group B and compared to the earlier 265 patients recorded as Group A in Table II. On the basis of experience and for tabulating convenience, the clinical groups are divided into the "serious" types (deep venous thrombosis, 102 in A, 90 in B; superficial and deep venous thrombosis, 13 in A, 21 in B; and embolism, source unknown, 11 in A, 12 in B) and "not serious" types (superficial venous thrombosis; 50 in A, 54 in B, and those suspected of having venous thromboembolism, 89 in A, 108 in B). Any patient with obvious or suspected venous thromboembolism who developed a sudden pleuritic chest pain while under observation was considered to have had a pulmonary embolism regardless of the absence of other confirmatory clinical or x-ray findings. Autopsies were obtained on 7 (69.2 per cent) of the 13 fatalities and all confirmed pulmonary embolism as the direct or indirect cause of death. The ages of the patients who died ranged from 44 to 87 years with the mean age at 67 distributed between 9 men and 4 women. Six were post-traumatic, 6 had cardiovascular disease as the main predisposing condition, and one was apparently spontaneous.

TABLE II. GROUPING OF TABLE I PATIENTS TO COMPARE PATIENT CHARACTERISTICS AND RESULTS OF METHODS OF MANAGEMENT

PERTINENT CHARACTERISTICS	GROUP A				GROUP B			
Number of patients	265				285			
Male	136 (51.3%)				154 (54.1%)			
Female	129 (48.7%)				131 (45.9%)			
Mean age	52 years				52 years			
Predisposing conditions	205 (77.3%)				226 (79.3%)			
Embolism	41 (15.4%)				55 (19.3%)			
Treatment over 15 days	27 (10.2%)				29 (10.1%)			
Clinical grouping (patients)	Serious (126)		Not serious (139)		Serious (123)		Not serious (162)	
ASRV grouping (patients)	Plus (80)	Minus (46)	Plus (61)	Minus (78)	Plus (57)	Minus (66)	Plus (28)	Minus (134)
Results								
Thrombosis	22	2	7	9	8	3	None	7
Embolism	21	5	3	None	5	6	None	None
Fatal	5	2	3	None	2	1	None	None

Comparison of Group A and Group B shows that the fatalities were reduced from 10 (3.7 per cent) to 3 (1.0 per cent), the incidence of embolism from 10.9 to 3.8 per cent, and that of thrombosis from 15.0 to 6.3 per cent. The

fatalities and thromboembolic complications due to inadequacy of clinical guides seem to have been eliminated by the addition of SRV observations. Two of the fatalities in Group B had contraindications to anticoagulant therapy; they were a 59-year-old woman with a fractured hip (ASRV –2) and a 76-year-old man with a myocardial infarction (ASRV +6). The other fatality was a terminal type 63-year-old man in the final phases of chronic cardiovascular disease, polycythemia, diabetes, and cirrhosis of the liver (ASRV +5). Both male fatalities had their emboli from endocardial mural thrombi. Thus, only one (0.35 per cent) in Group B was a venous thromboembolic death.

The thromboembolic complications in Group B were limited to treatment control lag (thrombosis 4, embolism 3) and obscure causes of vein wall inflammation (thrombosis 13, embolism 5). Eight of the thromboses in the latter group were in superficial venous thromboses and 2 were in cancer patients, who also sustained one of the emboli. The remaining 3 thromboses and 4 emboli were in patients who had long-standing venous thromboembolism.

The SRV observations have added another objective sign to the general impression that superficial venous thrombosis is a rather benign condition. Almost 80 per cent had minus ASRV, and there were no emboli or fatalities after these patients came under observation. Only 12.4 per cent received heparin therapy and 19.4 per cent had a high saphenous vein ligation while the remaining 68.4 per cent had anti-inflammatory or just symptomatic treatment in about equal numbers. The 25 extensions of thrombosis that occurred in the 104 patients were not significantly disabling and were distributed among all 4 types of treatment with the greatest number (36 per cent) occurring in the ligated group. While it appears that any of these forms of treatment will do, it must be kept in mind that the inflammatory process in the superficial veins can extend into the deep system and result in emboli as evidenced by the history of most of the 34 patients who had superficial and deep venous thrombosis when first seen (Table I). Thus, it would seem advisable to treat superficial venous thrombosis patients having plus SRV with anticoagulants. On the other hand, despite the fact that about half of the patients treated surgically developed an extension of the thrombosis up to the point of ligation, a high saphenous vein ligation is probably the treatment of choice in patients with venous thrombosis in varicose veins. The procedure is simple, minimizes hospitalization to one or 2 days, frequently gives the patient dramatic relief of pain and apprehension, and at the same time starts the treatment of the varicose veins.

There was a total of 197 patients only suspected of having venous thromboembolism at the outset and in none was it finally certain that the veins in the symptomatic calf were not primarily or secondarily involved in some degree of thrombosis or that the painful chest signs were not due to a small embolus. While all but 5 made an uneventful recovery suggesting that the thrombosis or embolism, if present, was usually not serious, the sudden embolic death in 3 who had only transient calf pain (ASRV +10, +14, +15) in Group A destroyed any remaining trust in clinical guides alone.

The 60 inadequately tested patients included 24 (40 per cent) with plus SRV and 36 (60 per cent) with minus SRV. This compares with the 41 per cent plus ASRV and the 59 per cent minus ASRV in the adequately tested 550 patients. Follow-up reports were obtained in 23 (63.8 per cent) of the minus group and in 17 (70.8 per cent) of the plus group. There was one death in each group and further thromboembolic complications in 4.3 per cent of the minus and 17.6 per cent of the plus group. Thus, the chance of a more serious case showing a plus SRV on the first test is fairly good. However, single tests are not adequate guides, particularly if they give minus results.

It will be noted that while Groups A and B are quite similar as to clinically "serious" cases, the ASRV are quite different; Group A had 141 (53.2 per cent) plus ASRV while Group B had only 85 (29.8 per cent) plus ASRV. Since treatment is not thought to affect the SRV on which these averages were based, the better results in Group B may not necessarily be due to therapy but rather to the possibility that the group happened to consist of patients who had a better prognosis to begin with; this finds some support in the similar 10-year experience results in 511 patients with venous thromboembolism treated with anticoagulants reported by Coon.[3] Attempts to correlate the ASRV differences in the groups to such likely variations as sex, age, predisposing conditions, pretreatment embolism, and duration of illness before treatment were fruitless. Whatever the cause, this group difference in ASRV and results further emphasizes the need for some blood index as SRV for the more complete evaluation of a patient with venous thromboembolism.

SUMMARY

The most important result of this routine of management has been the clearing of the uncertainties that clouded decisions of diagnosis and treatment in the uneasy situations that can be presented by venous thromboembolism. This was particularly true in the patients only suspected of having venous thrombosis or embolism where the giving or withholding of specific treatment has been made more certain. There were no such fatalities in Group B (Table II) as contrasted with the 3 fatalities in Group A. There was no need to try to differentiate between thrombophlebitis or phlebothrombosis. The selection of the type of treatment and its duration was no longer fettered with doubt in either the suspected or obvious case of venous thromboembolism. Heparin has proved to be a very satisfactory and safe drug which requires very little or no laboratory control and the only anticoagulant necessary in 90 per cent of the patients needing such treatment. The more meticulous attention demanded by Dicumarol was reserved for the 10 per cent that required treatment for more than 2 weeks. Deep venous ligation was narrowed down to the rare patient in whom anticoagulant therapy has honestly failed. Superficial venous thrombosis has been further tagged as a usually benign condition and treatment in most cases need not be directed against the clotting mechanism. It has reduced anticoagulant therapy to 60 per cent of patients

with known or suspected venous thromboembolism and this for less than 2 weeks while the remaining 40 per cent received nonspecific treatment for about 1 week. This is in contrast to the 2 to 6 weeks of anticoagulant therapy for venous thromboembolism in general use. This reduction in the period and type of treatment has been associated with a drop in mortality to 0.3 per cent for venous thromboembolism or to 1.0 per cent, if all fatal pulmonary emboli, irrespective of source, are considered. This method, in attempting to estimate the factors involved in thromboembolism, provides a more precise selection of patients for specific therapy which not only safely minimizes the period of disability but also focuses attention on those that need revisions of existing therapy or the finding of new treatments.

CONCLUSIONS

1. The need to approach the clinical problems presented by venous thromboembolism by appraising the cause of venous damage, blood composition changes and stasis in each case is emphasized.

2. A blood drop test for determination of blood composition changes is briefly presented and means for estimating venous damage and stasis are discussed.

3. A routine of management of a patient with suspected or obvious venous thromboembolism based on observations on 298 patients is presented.

4. The results of the application of this routine of management on 285 patients indicate that it (a) helps dispel much of the doubt from uncertain clinical situations associated with venous thromboembolism, (b) more definitely outlines the types and duration of treatment and safely minimizes the period of necessary observation to less than 2 weeks in 90 per cent of the patients and indicates the need for anticoagulant therapy in only 60 per cent of the patients, and (c) isolates for concentrated attention those patients requiring prolonged, meticulous treatment and those for whom new treatments should be found.

ADDENDUM

Fifty-six more patients (30 "serious," 26 "not serious") have been added to Group B since this paper was prepared for publication. There have been no thromboembolic fatalities and only two minor pulmonary infarctions in this additional group.

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RUPTURED ABDOMINAL AORTIC ANEURYSM

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A REVIEW of the literature reveals many successful series of resected and replaced intact abdominal aortic aneurysms since Dubost's "first" in 1951.[5] Few reports are available, however, with respect to ruptured abdominal aneurysms. Many of the latter are of single cases; others are of selected series from specialized centers.[3, 6, 8] From January, 1956, to December, 1958, 28 ruptured aortic aneurysms were seen by the authors. These were all frank ruptures with recent retroperitoneal hemorrhage. Three were operated on but the patients died before completion of the procedure. In 4 no surgical therapy was attempted. The remaining 21 were resected and replaced by grafts; these are the main topic of this presentation.

The following describes the 3 patients subjected to operation who died before a graft could be inserted:

Case 1.—The patient was a 78-year-old man in complete collapse of 5 hours' duration. There was a large, and visibly enlarging, hematoma. Despite prompt interference the patient died 20 minutes after the incision was made.

Case 2.—A 73-year-old man with a past history of coronary occlusion and pulmonary tuberculosis had been in partial collapse for 24 hours. Collapse was complete just prior to commencement of the operation. Aortic control improved his condition and graft replacement was under way when he died on the operating table. Autopsy revealed an old and a recent myocardial infarct.

Case 3.—A 76-year-old man collapsed following cystoscopy and fulguration of a bladder tumor. Resuscitative efforts, including 4 pints of blood, produced no response. With a probable diagnosis of ruptured aneurysm and a possible diagnosis of perforated bladder, laparotomy was undertaken. A large aneurysm was found to be perforated anteriorly. Hemorrhage was controlled by a sutured patch of rectus muscle over the opening. Further transfusion was to no avail and the patient died one-half hour postoperatively. Autopsy showed no evidence of continued hemorrhage.

The 4 patients in whom the diagnosis was made of ruptured aneurysm, but in whom operation was not attempted, are herewith summarized:

Case 1.—An elderly man, in whom a ruptured aneurysm of the upper abdominal aorta at the level of the superior mesenteric and renal arteries was diagnosed clinically and corroborated by aortography and autopsy, died within 12 hours. Successful resection of a similar but intact aneurysm has since been reported.[4]

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CASE 2.—An elderly man with cancer of the prostate and metastases had a ruptured abdominal aneurysm. He died in 3 days without operation.

CASE 3.—An elderly lady with marked senile deterioration, physical and mental, who was confined to a nursing home, was admitted in collapse with a ruptured aortic aneurysm. She died without operation in 48 hours.

CASE 4.—A 75-year-old man, chronically hospitalized with asthma, cardiac disease, and prostatism, was seen, 5 days after rupture, in extremis. With only medical supportive treatment he died in 36 hours.

Not included in the group under discussion are "acute" abdominal aneurysms. There were 3 such cases encountered in the same period. We consider them a distinct entity worthy of some comment. Differentiation from a ruptured aneurysm may be difficult or impossible; it is not essential. We believe operation is urgently indicated to forestall imminent rupture. This urgency was substantiated by the first of these cases, that of a 73-year-old obese woman who presented with ileus and a large, acutely tender aneurysm. Laparotomy confirmed the ileus but the aneurysm was found intact. After debate, resection was not performed. It was hoped that the patient's condition might improve and other possible causes for ileus be eliminated. However, the abdominal pain and ileus persisted until she died abruptly 10 days postoperatively of frank aneurysmal rupture. The second case was that of an 84-year-old man (our oldest patient) who was submitted to laparotomy with the diagnosis of "acute" aneurysm. This was resected and replaced with a crimped nylon graft. He is alive and well 12 months after operation. The third patient had sudden severe pain in the abdomen and back and was found to have an intact aneurysm. This was resected and replaced with a graft. His postoperative course was eventful only for the development of a "seroma" which required drainage. He is alive and well.

It is to be noted that the above represents all the ruptured aneurysms seen by the authors during this period. These were all treated at 4 hospitals: the Vancouver General, St. Paul's, and Shaughnessy in Vancouver, and the Royal Columbian in New Westminster. Only 2 patients were transferred from an adjacent hospital for treatment. None traveled more than a very short distance. Only in the most debilitated patients was no effort made at salvage. Hypertension, previous cardiac infarcts, cerebrovascular accidents, asthma, arthritis, and other diseases were not considered contraindications. In fact, a history of one or more such conditions was the rule rather than the exception. Nor was profound shock or massive hematoma a contraindication. Shock of a degree which made blood pressure reading difficult or impossible by the anesthetists at the commencement of the operation was present in 13 of the 21 resected cases.

The remainder of this paper will be confined to the 21 cases of frankly ruptured aneurysm in which resection and replacement by grafts were done (Table I).

TABLE I, *A*

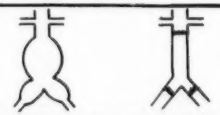
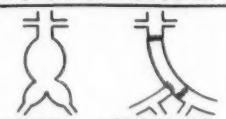
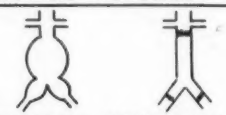
CASE NO.	DATE	AGE SEX	ACUTE HISTORY	HOURS DURATION PRE-OP.	OPERATION	BLOOD ADMIN.	COMPLICATIONS	RESULT
1.	JAN. 28 1956	71 ♂	4:00 P.M. ABDOMINAL PAIN. WEAKNESS WITH VOMITING & DIARRHOEA. PAIN – EPIGASTRIC – LATER TO BACK. COLLAPSE	20	 BIFURCATION HOMOGRAFT	11	OLIGURIA – NPN – 225. BRONCHITIS, MUSCLE SPASM, DIARRHOEA	GOOD POPLITEAL PULSES. DIED. OCT 6/58 (33 MOS.) RUPTURE OF GRAFT INTO DUODENUM
2.	JUNE 16 1956	83 ♂	JUNE 15, P.M. PAIN. JUNE 16 – 3:00 A.M. PAIN, COMPENSATED SHOCK. JUNE 16 – 11:00 A.M. OPERATION PRE-OP. COLLAPSE	18	 THORACIC HOMOGRAFT	9	MILD OLIGURIA – CVA	GOOD PERIPHERAL CIRCULATION. DIED 8th POST-OPERATIVE DAY CVA
3	JULY 17 1956	67 ♂	BACK PAIN – 8:00 A.M. COLLAPSE – 4:00 P.M. COLLAPSE – 7:00 P.M. OPERATION – 11:00 P.M.	15	 THORACIC HOMOGRAFT	10	OLIGURIA. ISCHAEMIC NECROSIS OF CALF MUSCLES	DIED 12 HOURS POST-OPERATIVELY
4	OCT. 3 1956	52 ♂	TEARING PAIN LOWER ABDOMEN & LUMBAR, ESPECIALLY RIGHT LOWER QUADRANT	3½	THORACIC HOMOGRAFT	7	NONE	ALIVE GOOD PULSES
5	JAN. 9 1957	65 ♂	PAIN IN BACK THEN TO LOWER ABDOMEN	13	HOMOGRAFT BIFURCATION	5	BRONCHITIS	ALIVE GOOD PULSES
6	FEB. 22 1957	71 ♂	PAIN IN UPPER ABDOMEN. GRADUALLY COLLAPSED JUST PRIOR TO OPERATION	5	THORACIC HOMOGRAFT	6	NO RIGHT FEMORAL PULSE 1 HOUR POST-OP. THROMBOENDARTERECTOMY RIGHT COMMON ILIAC	ALIVE GOOD PULSES
7	MAR. 6 1957	♂	VERY SUDDEN SHARP STABBING PAIN, LEFT LUMBAR AREA TO LEFT HYPOCHONDRIUM. VOMITED ONCE – COLLAPSE	7	THORACIC HOMOGRAFT	6	LEAKAGE IN UPPER ANASTOMOSIS – 3 HOURS POST-OP.	DIED FROM LEAKAGE 3 HOURS POST-OPERATIVELY

TABLE I, *B*

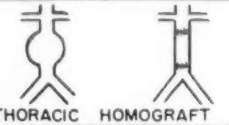
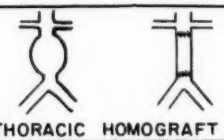
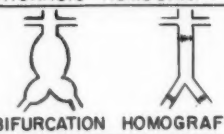
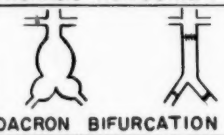
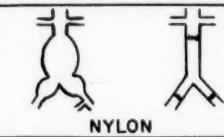
CASE NO.	DATE	AGE SEX	ACUTE HISTORY	HOURS DURATION PRE-OP.	OPERATION	BLOOD ADMIN.	COMPLICATIONS	RESULT
8	MAY 23 1957	64 ♂	ABDOMINAL PAIN, DIARRHOEA, COLLAPSE & ENLARGING MASS	24	THORACIC HOMOGRAFT.	10	TRACHEOTOMY, URINARY OUTPUT SATISFACTORY. VENTRICULAR TACHYCARDIA, PYELO-NEPHRITIS-3 WKS. POST. OP.	GOOD GENERAL & PERIPHERAL CIRCULATION. ALIVE & WELL
9	MAY 28 1957	82 ♂	SEVERE ABDOMINAL PAIN	4	THORACIC HOMOGRAFT RT. COM. ILIAC	8	SPLENECTOMY, EVISCERATION, PHLEBITIS, OLIGURIA	DIED 7 DAYS POST-OP. PULMONARY OEDEMA
10	JUNE 18 1957	52 ♂	SEVERE RIGHT LOWER QUADRANT PAIN:-TO LUMBAR -TO HIPS	51	THORACIC HOMOGRAFT	9	BRANCHES OF LEFT RENAL VEIN TORN. BILATERAL RENAL INFARCT	DIED 48 HOURS IRREVERSIBLE SHOCK
11	JULY 26 1957	57 ♂	9:15 A.M.-ADMITTED - 2:30 P.M. COLLAPSE - 2:30 A.M. OPERATION. HUGE ABDOMINAL ANEURYSM & LEFT SIDED HAEMATOMA	12	THORACIC HOMOGRAFT	14	FAILED TO RESPOND FROM COMPLETE COLLAPSE	DIED 2 HOURS POST-OPERATIVELY
12	JULY 30 1957	64 ♂	SEVERE SUDDEN EPIGASTRIC PAIN	3	THORACIC HOMOGRAFT	6	B.P. FELL WHEN AORTIC CLAMP RELEASED. CONTINUED TO FALL IN SPITE OF RE-CLAMPING & DIED	DIED
13	OCT. 2 1957	69 ♂	SEVERE PAIN LEFT LOWER QUADRANT TO PENIS. C.C. PAIN IN PENIS & GROINS	42	TEFLON BIFURCATION GRAFT	9		DIED 20 HOURS POST-OPERATIVELY
14	NOV. 3 1957	72 ♂	SEVERE PAIN IN LEFT HIP & LEFT TESTIS	3½	 THORACIC HOMOGRAFT	18	FIRST HOMOGRAFT NECROTIC, REPLACED WITH SECOND HOMOGRAFT	DIED - 1½ HOURS POST-OP. SHOCK

TABLE I, C

CASE NO.	DATE	AGE SEX	ACUTE HISTORY	HOURS DURATION PRE-OP.	OPERATION	BLOOD ADMIN.	COMPLICATIONS	RESULT
15	APR. 23 1958	64 ♂	SUDDEN, LOW BACK, TO ABDOMEN	4½	 THORACIC HOMOGRAFT	6	EVISCERATION 7th. POST-OPERATIVE DAY	DIED AFTER OPERATION FOR EVISCERATION - OVERDOSE OF CURARE
16	APR. 29 1958	75 ♂	SEVERE ABDOMINAL PAIN	10	 BIFURCATION HOMOGRAFT	7	BILATERAL PAROTITIS	DIED NOV. 3rd. 1958 RUPTURE OF GRAFT INTO DUODENUM
17	JULY 29 1958	63 ♂	SUDDEN SEVERE PAIN, RIGHT LOWER QUADRANT	7	THORACIC HOMOGRAFT	6	SEVERE OLIGURIA 100-250 cc/DAY FOR 7 DAYS. JAUNDICE, STAPH. PNEUMONIA, SUBDIAPHRAGMATIC ABSCESS, ACUTE NEPHROSIS	DIED 19th POST-OPERATIVE DAY
18	SEPT 26 1958	70 ♂	24 HOURS PAIN COLLAPSE PRE-OP.	24	 DACRON BIFURCATION	14	ANOREXIA, BRONCHOPNEUMONIA, TRACHEOTOMY	DIED NOV 17th 1958 GENERAL DETERIORATION
19	OCT. 19 1958	74 ♂	SEVERE ABDOMINAL PAIN		CRIMPED KNITTED DACRON		BRONCHITIS, CARDIAC FAILURE, EVISCERATION, SMALL BOWEL OBSTRUCTION	ALIVE 100 DAYS POST-OPERATIVELY
20	OCT. 25 1958	62 ♂	PAIN RIGHT GROIN, COMPENSATED SHOCK, X-RAY DIAGNOSIS	18	 NYLON	10	OLIGURIA, MUSCLE NECROSIS RIGHT	DIED 48 HOURS
21	DEC. 19 1958	64 ♂	SUDDEN SEVERE PAIN IN EPIGASTRIUM & DOWN LEFT SIDE — SHOCK —	48	DACRON	5	NO COMPLICATIONS EXCEPT MENTAL CONFUSION	DISCHARGED 13th DAY. ALIVE 37 DAYS POST-OP.

DIAGNOSIS

In most instances the diagnosis of ruptured abdominal aneurysm was made with ease as the examiner gained experience. Most commonly, severe abdominal and/or back pain preceded collapse. Symptoms referable to the genitourinary or gastrointestinal tract were commonly recorded and would seem to be related to the direction in which the hematoma dissected. The general appearance of the patient—pallor, apprehension, and clammy extremities—was indicative of a catastrophe. Abdominal examination revealed no rigidity, a large tender aneurysm, and frequently an expanding mass in the abdomen or iliac fossa. The diagnosis was not always readily made and valuable time was lost before operation. This was indicated by the interval, in the 21 grafted cases, from the onset of symptoms to the time of operation—a minimum of 3 to a maximum of 51 hours, with a mean of 12 hours. Much of this delay was of doctor origin and was caused by atypical findings which misled the examiner, e.g., 2 cases with pain referred to the genitals (Cases 13 and 14). Also misleading was the period of compensated shock which most of these patients displayed. Collapse was usually imminent and, when it occurred, was profound.

Fig. 1.—Lateral view of the abdomen in Case 19. Note profile of the ruptured aortic aneurysm with overlying distended bowel loops.

In some thickset or obese patients, the diagnosis may be difficult in that the aneurysm and hematoma may be neither visible nor palpable. X-rays of the abdomen are then helpful; in particular, a lateral view, which profiles the aneurysm. In Case 19, a very obese man, the x-ray was diagnostic (Figs. 1 and 2).

Additional signs have been noted as being of diagnostic import. An interesting report found a change in deep tendon reflexes and bloodstaining in the flank or groin to be useful aids to diagnosis.[1] We have not noted the former and consider the latter a late and, therefore, relatively less valuable sign. If

ruptured aneurysm had been included in the differential diagnostic list of abdominal catastrophes, most of these cases would have been recognized earlier. Acute pancreatitis, mesenteric vascular occlusion, coronary occlusion with abdominal symptoms, and renal colic must be excluded.

MANAGEMENT

Preoperative.—When the diagnosis is made, immediate cross-matching for 4 to 5 liters of blood and transfer of the patient to the operating room is indicated. Frequently the patient is deceptively well, yet evidence of shock will be found by the careful examiner. Commonest signs are clammy perspiration and cold extremities. Early in the series some delay was accepted. Experience has taught us that collapse may occur at any moment and, in fact, it did in most of these patients before operation was begun. This infinitely worsens the prognosis. Transfusion and other means of resuscitation will not be effective and, in fact, may precipitate further hemorrhage. Such efforts should be incidental to the prime objective—aortic control.

Fig. 2.—Anteroposterior view of patient in Fig. 1, showing clear outline of the ruptured aneurysm.

In the operating room, preparation for operation should proceed directly. The abdomen is prepared from nipples to midthigh, a retention catheter is inserted, oxygen is administered, and large (No. 16) needles or cannulae are inserted into upper extremity veins.

Operative.—The incision must be generous and one quickly made and closed. A midline xiphoid-to-pubis incision best answers these criteria. Paramedian

incisions have also been used with satisfaction and in one very obese patient a transverse incision of heroic length was used. It is important to have control of the aorta above the aneurysm. This can be achieved through an abdominal incision. We feel that thoracotomy is unnecessary and undesirable. If the patient is in severe collapse, the abdominal aorta may be located between the crura of the diaphragm and compressed digitally against the vertebral column. A padded wooden compressor (Figs. 3 and 4) can be substituted for the fingers and dissection proceed. There will usually be prompt improvement in the condition of the patient.

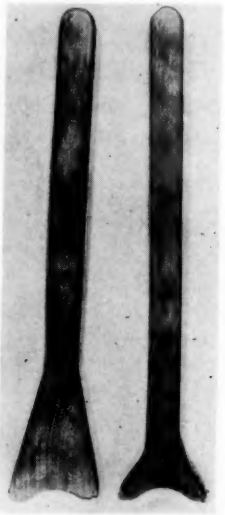


Fig. 3.

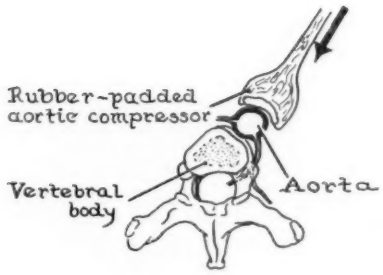


Fig. 4.

Fig. 3.—Wooden aortic compressors with sponge-rubber pads used in emergency aortic control.

Fig. 4.—Diagram representing the use of the compressor.

If the patient's condition and the absence of bleeding permit, more deliberate dissection is carried out. The small bowel is packed out of the abdominal cavity and, through a peritoneal incision to the left of the small bowel mesentery, the proximal aorta is cleared. This dissection is often done blindly because of the bulk of the aneurysm and extravasated blood. A clamp is placed about the aorta but not closed. During this dissection it is desirable to define the renal vein and mobilize it upward under a narrow Deaver retractor. Next, the common iliac arteries are defined and cleared. Heparin, 30 to 50 mg., is introduced into the aneurysm and the aortic and iliac clamps are closed.

Removal of the aneurysm and hematoma is not a delicate procedure. The aneurysm is first evacuated of clot and pultaceous material. The wall is removed piecemeal with stout forceps and scissors. Caution is advisable in the vicinity of the inferior vena cava and left iliac vein as it crosses the midline. Usually a strip of aneurysmal wall is left attached to these fragile structures. Efforts at meticulous dissection have been costly in time and blood loss—two precious commodities in this procedure. The inferior mesenteric artery is routinely sacrificed; it is ligated close to its origin from the aorta to preserve the valuable left

colic–superior hemorrhoidal anastomosis. No trouble was experienced with circulation in the left colon. Proximally, the aorta is separated from the vena cava and distally the iliac artery from the corresponding veins. At each site the vessel is trimmed to obtain the most normal available tissue; the ideal is to obtain a 1 cm. cuff beyond the clamp. As the proximal aorta is cleared, the renal arteries are defined and better placement of the proximal clamp may be achieved.

Most cases require anastomoses to the iliac vessels. In a few, a single anastomosis to a relatively normal aortic bifurcation is possible. All anastomoses are fashioned with 5-0 silk. When the proximal anastomosis is completed, the suture lines are tested by release of the aortic clamp while the graft is controlled. At this stage both anterior and posterior suture lines can be inspected freely and repaired easily. Just before the distal anastomoses are completed, the graft is flushed with blood from above to clear debris and clot. As soon as one distal anastomosis is completed, blood is allowed to flow down this side to restore some circulation to the lower extremities. Release of the aortic clamp often results in a marked pressure drop necessitating intermittent re-application until the patient's condition is stabilized.

Homografts were used in 15 cases, prosthetics in 6 (nylon 2, Dacron 3, Teflon 1). We are currently using prosthetic materials (in particular, Teflon) exclusively. We have found the latter satisfactory and much more convenient than homografts. In addition, we have been concerned about late changes in the homografts (see below).

The peritoneum over the aneurysm is closed with a running catgut suture. It is desirable to bring peritoneum between the duodenum and proximal anastomosis. Duodenal adherence to the proximal anastomosis with erosion and gastrointestinal hemorrhage has been reported[2] and we had a similar experience in 2 cases in this series (Cases 1 and 16).

Closure of the abdomen is simple but must be strong. Evisceration of these huge wounds in elderly people is common. Closure consists of continuous and interrupted chromic catgut for the peritoneum and interrupted wire in the fascia. There is undoubtedly a place for through-and-through wire closure and the authors will probably use this more frequently, both for speed and for security.

Supportive treatment throughout and immediately after resection of the ruptured abdominal aneurysm is important. A placid anesthetist is a great asset in dealing with a situation where the patient, at the outset, may be without recordable blood pressure—a common phenomenon which tends to recur during the procedure. Minimal anesthetic agent and maximal oxygen are desirable. Replacement therapy is best done into the upper extremities where blood flow is uninterrupted. One or, better, two No. 16 needles or cut-downs are used. Transfusion is limited until the aorta is controlled. Control of the aorta alone produces prompt improvement in the patient's condition. A rough estimate of the blood loss into the hematoma is made and this quantity of blood is rapidly infused. Subsequent blood losses are matched as the operation proceeds. Solu-Cortef, given intravenously, has impressed us as being valuable in severe shock

or in shock resistant to control of the aorta and transfusion. In some cases 100 to 500 mg. was given during the operation with decreasing amounts given during the postoperative period.

Postoperative.—Standard measures postoperatively include gastric suction until peristalsis is restored, retention catheter, careful fluid balance, and correction of hemoglobin deficiencies as determined at 24 and 72 hours. Penicillin and streptomycin are given for 5 to 10 days. Problems which particularly require attention include oliguria and retained bronchial secretions. The latter are common in these aged patients subjected to a very stressing procedure. Tracheotomy was performed several times for patients unable to clear their secretions.

COMPLICATIONS

Early.—

Impaired circulation to the legs: This was less a problem in aneurysmal than in occlusive disease. The vessels were large and generous anastomoses could be made. Still, some cold legs were seen in the immediate postoperative period. A loosened plaque or thrombus was usually the cause, and immediate exploration was performed. Femoral explorations under local anesthesia added little stress and proved successful in 2 such problems. Preventive measures thought important are securement of the intima, flushing out of the graft, introduction of heparin prior to aortic clamping, and rapid restoration of lower extremity circulation.

Renal shutdown: This complication occurs in elective resections for abdominal aortic aneurysm. The ruptured aneurysm, in the presence of which shock is a prominent feature, is even more susceptible. Most of this group of patients had oliguria and elevated nonprotein nitrogen postoperatively. Five of 10 surviving long enough for renal function to be ascertained had severe oliguria, for which the most cautious fluid and electrolyte control was necessary. One patient received too much fluid and died of pulmonary edema. At present, moderate hypothermia is being used to protect the renal tubules. The introduction of local anesthesia about the aorta and renal arteries, with a view to inhibiting spasm and tubular necrosis, is being tried.[8]

Other vascular complications: Unquestionably, these patients had extensive atherosclerosis. The aneurysm was but one manifestation. One patient had a cerebrovascular accident on his seventh postoperative day and an extension of this resulted in his death on the eighth day. Another patient went into partial collapse on the eighth postoperative day with a persistent ventricular tachycardia which finally yielded to digitalis and quinidine.

Abdominal complications: Despite the extensive incision and prolonged evisceration, ileus and mechanical obstruction have been unusual. Most of these patients had active bowel sounds and passage of flatus in 48 hours. One patient was subject to recurring mechanical small bowel obstruction. Laparotomy revealed an adhesion to the posterior peritoneal closure.

Wound problems were relatively frequent. Many showed a minor degree of infection or necrosis. In 3 there was frank evisceration; 2 of these patients

died. In the survivor, the evisceration was repaired under local infiltration anesthesia with through-and-through No. 30 wire. These gravely ill patients tolerated additional general anesthesia poorly.

Late.—Three patients died of complications at 52 days, 6 months, and 33 months, respectively.

Pulmonary: One patient (Case 18) had been in the hospital for 8 weeks with bronchopneumonia and rheumatoid arthritis. He had been treated with antibiotics and cortisone with sufficient success to ready him for discharge to a nursing home when rupture of an abdominal aneurysm occurred. This was successfully resected and replaced with a Dacron bifurcation graft. Postoperative bronchial secretions were excessive and tracheotomy was performed. Once again he was painfully rehabilitated but he remained incapable of handling his bronchial secretions. Although he survived the operation and the immediate postoperative period, he died abruptly 52 days after operation. Autopsy revealed the graft to be in excellent condition (Fig. 5) but there was bilateral bronchopneumonia and an early lung abscess.

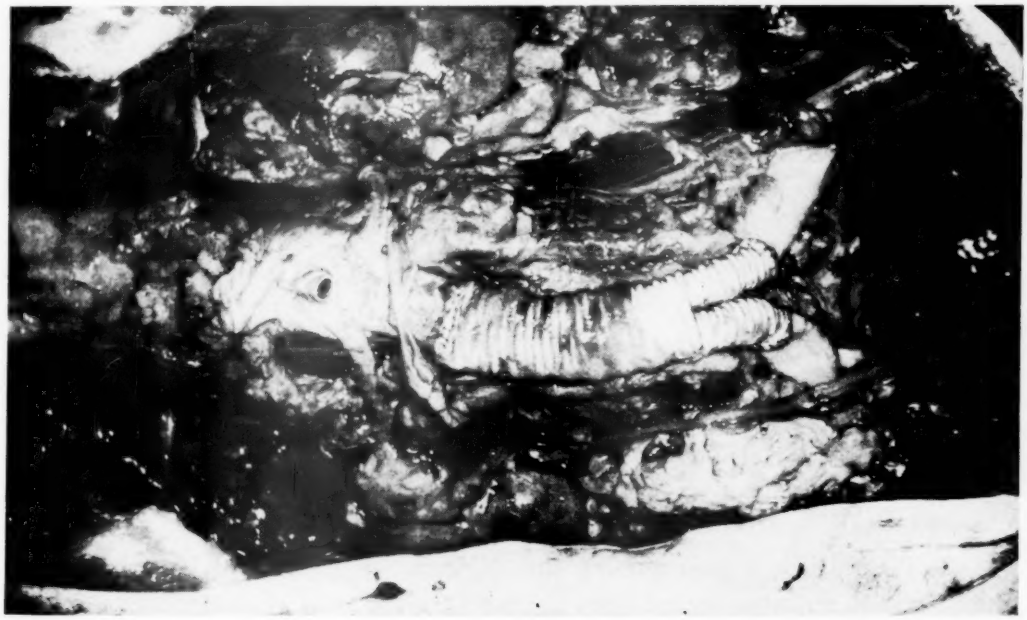


Fig. 5.—Autopsy findings in Case 18 when the patient died 52 days postoperatively of pneumonia. All suture lines were intact. The Dacron graft inside and out was covered with a dense, tough layer of fibrous tissue which peeled off with difficulty. In this illustration the layer has been peeled off the lower half of the graft. Note left renal vein running above proximal anastomosis.

Graft: Two patients (Cases 1 and 16) died of an unusual but previously reported complication—ulceration of the proximal anastomosis into the duodenum with fatal hemorrhage. In Case 1 this occurred 33 months after operation; in Case 16 it was 6 months after operation. In both cases, homografts were used to replace the aneurysm and although this complication may also occur with prosthetics it is difficult to completely exonerate the homografts.

The homograft which had been in place for 33 months showed extensive arteriosclerotic change. This finding has further strengthened our desire to use prosthetics. This experience has also recommended to us the advisability of separating the suture line in the graft from the gastrointestinal tract with a layer of peritoneum.

CONCLUSIONS

1. Twenty-eight frankly ruptured abdominal aortic aneurysms were seen by the authors in a 2-year period. Only 4 were considered inoperable. A further 3 patients died during the course of operation. Twenty-one had the aneurysms resected and replaced by grafts. The experience with these comprises the substance of this report. There were 9 survivors beyond the 1-month postoperative period.

2. Three acute but intact aneurysms were considered a separate entity and are briefly described.

3. The majority of the 21 patients in whom resection was done suffered from serious coincidental disease. Thirteen were in complete collapse prior to operation.

4. Diagnosis of the ruptured aneurysm was made readily with experience. There was considerable delay prior to referral, indicative of diagnostic difficulty in the profession generally. Ruptured aneurysm should be added to the differential list of abdominal catastrophes.

5. Immediate operation and aortic control were the most important considerations in treatment. Delay only invited collapse. Other resuscitative measures proved to be of incidental importance.

6. The technique of the abdominal operative procedure is reviewed. Highlights in our experience were the use of an aortic compressor to obtain proximal control and the piecemeal excision of the aneurysm with a protective patch left on vulnerable veins.

7. Immediate postoperative complications encountered were impaired leg circulation, oliguria, evisceration, other arteriosclerotic catastrophes, and mechanical small bowel obstruction.

8. Two late complications of the replacement procedure were erosion of the proximal anastomosis into the duodenum with fatal gastrointestinal hemorrhage. These occurred at 6 and 33 months, respectively. The homograft in the latter case showed marked arteriosclerotic degeneration and this experience, as well as the availability of prosthetics, has accounted for our present preference for the latter.

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Pediatric Surgery

CONDUCTED BY MARK M. RAVITCH, M.D.

GASTROSCHISIS

A METHOD OF TREATMENT

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GASTROSCHISIS is a rare congenital malformation in which the abdomen remains open. This is thought to be due to incomplete fusion of the right and left ventral myotomal masses, as they replace the somatopleure to form the true body wall, at about the end of the twelfth week of intrauterine life.[1]

The opening in the abdominal wall is usually to one side of, and on a level with, the umbilicus, but does not involve the cord which is normally inserted. Most commonly cord structures form a part of its circumference, but there may be separation by skin.[7] The defect is round or oval, and from 1 to 10 cm. in diameter.[3, 6] There is no membranous covering or remnant of a sac, as with a ruptured omphalocele from which it must be differentiated. The eviscerated mass of intestines represents all or a portion of the embryonic mid-gut which has also failed to rotate. Other organs such as the gall bladder and uterus may protrude through the larger defects. The displaced structures are discolored, edematous, covered with vernix caseosa, and matted together by fibrinous exudate. The capacity of the abdominal cavity tends to vary inversely with the size of the eviscerated mass. The relative disproportion between these seems to have drawn the line between therapeutic success and failure in the past.[5, 8]

All of the therapeutic successes to date[1, 2, 5, 8] have been with cases where minimal disproportion between the size of the eviscerated mass and the capacity of the peritoneal cavity made it possible to reduce the mass and to do a more or less complete primary abdominal wall closure. Berman[1] was able to do this after reducing the disproportion by resecting jejunum, ileum, and right colon. Hardaway[5] closed only the skin after undermining for a few centimeters, but the disproportion was relatively slight. Moore and Stokes[7] applied Gross's technique[4] to 2 patients showing marked disproportion, but unfortunately both died of pulmonary complications, leaving unknown the subsequent course of events with this approach.

This paper reports the successful application of skin closure to a case of gastroschisis with marked disproportion, describes the surgical problem which remained, and presents a possible solution of this second obstacle to complete abdominal wall repair.

Received for publication Feb. 6, 1959.

CASE REPORT

The parents of the patient were both 27 years of age and of Caucasian stock. Their two previous pregnancies had resulted in normal single births. There was no family history of congenital abnormalities. The mother's last menstrual period had started on Feb. 1, 1956, and the expected date of confinement was computed to be Nov. 8, 1956. Quickening was thought to have been noted during April. No exanthematous disease was noted during pregnancy.

The patient (P. J. F.) was born at 7:15 A.M. at the U. S. Army Hospital, Fort Bragg, N. C., on Oct. 23, 1956, weighing 4 pounds, 10¼ ounces, after a gestation of approximately 37 weeks. Labor was spontaneous in onset, normal in progress, and of 6 hours 15 minutes' duration. Delivery was by vertex presentation and uncomplicated. The placenta appeared to be normal.

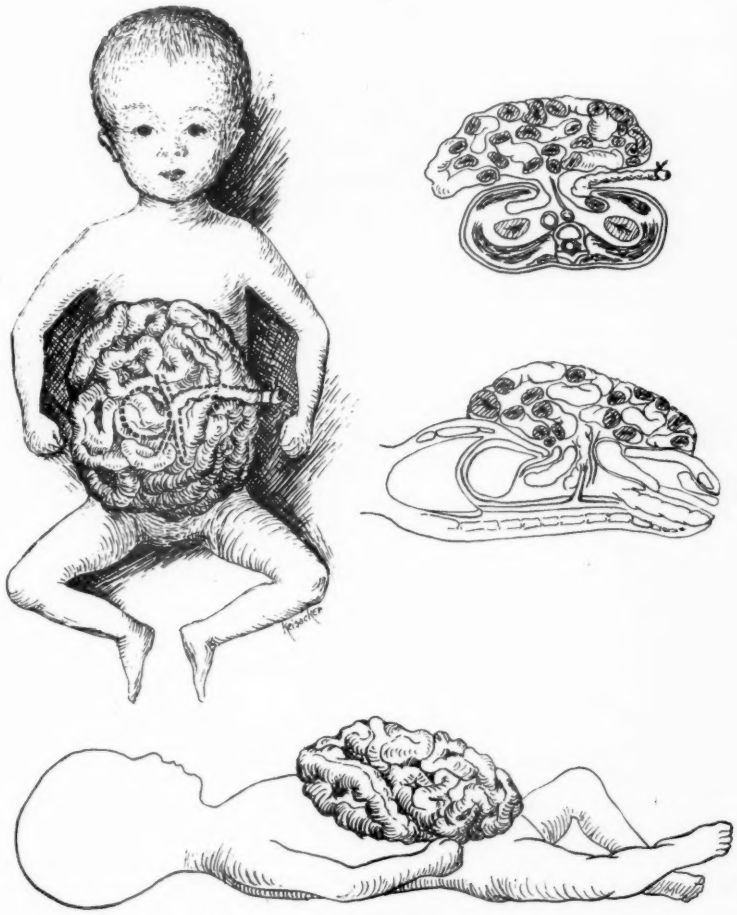

Fig. 1.—Appearance at birth.

Evisceration of the bowel was immediately noted by the obstetrician who wrapped the infant in sterile linen and sent her to the operating room after telephone consultation. This fortunately enabled me to undertake the surgical treatment within approximately 1 hour of birth.

The patient was a premature, white, female newborn infant with massive evisceration through a complete abdominal wall defect (Fig. 1). Lying on the abdomen were the gall bladder, part of the stomach, the jejunum, ileum, cecum, ascending and right transverse colon, and the uterus and its adnexa. The exposed organs were discolored, edematous, matted together by fibrinous adhesions and covered with vernix caseosa, but appeared viable. There

was no covering membrane or abnormality of the umbilical cord. The defect was round, approximately 5 cm. in diameter and immediately to the right of the normally inserted cord. Its edge was gray, smooth, and rounded where the skin and peritoneum fused without vestige of a membrane. The umbilical vein and right umbilical artery formed a part of its medial circumference. The abdominal wall was scaphoid and pressed against the retroperitoneal organs which seemed to fully occupy the diminutive peritoneal cavity. Despite this, the infant was in satisfactory general condition without gross evidence of other abnormalities.

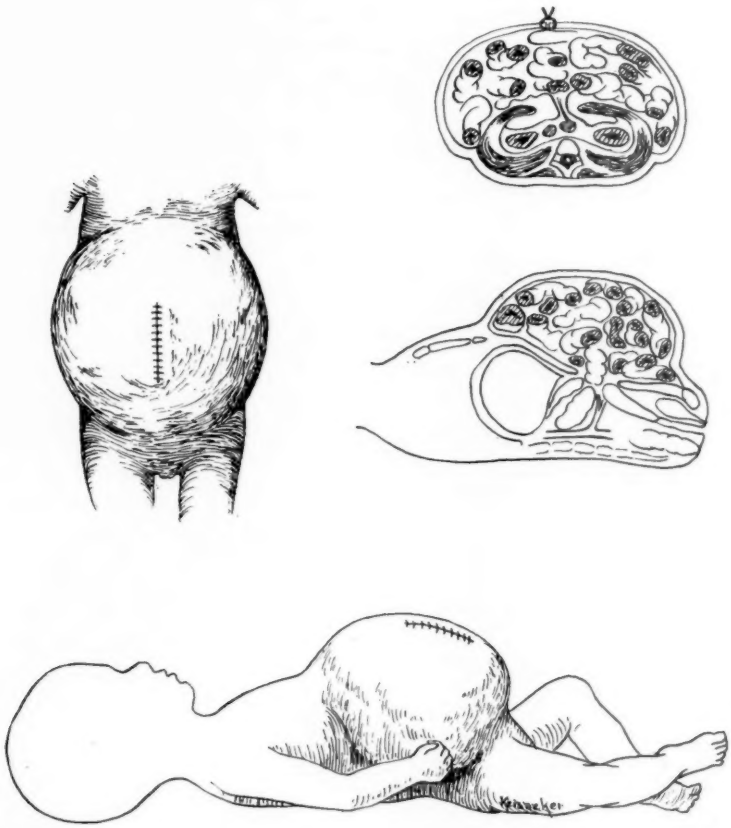

Fig. 2.—Appearance after skin closure, illustrating the new problem.

It was immediately apparent and quickly verified that reduction of the intestines was impossible. The gall bladder, stomach, and uterus were reduced, but only the stomach remained within the cavity. Since there was no constriction about the narrow stalk of the nonrotated mid-gut any enlargement of the defect appeared meddlesome. The umbilical cord was excised and its vessels individually ligated. A circumferential incision was made about the margin of the defect, freeing the skin which was then undermined by scissors and blunt dissection to the xiphoid above, symphysis below and the back on both sides. The skin was then drawn over the eviscerated mass and its opening was closed vertically with interrupted sutures of 4-0 silk forming a large ventral false hernia with prominent flank bulges (Fig. 2). Oxygen was administered during the procedure, but no anesthetic agent, blood, or parenteral fluid was given. The child's general condition was unchanged postoperatively and she was returned to the nursery within two hours of birth.

Back in the nursery, oxygen, with the addition of water mist, was continued until the following day. Penicillin and streptomycin were given. Small glucose feedings were started the day after surgery, but were poorly retained until the third day when normal meconium

stools were passed and the abdomen became soft. The following day, dilute formula feedings were started and retained well. By the sixth day the baby's condition appeared stable. Her weight fell to a low of 4 pounds, 5½ ounces on the eighth day, but had exceeded the birth figure by the seventeenth day. All sutures had been removed by the thirteenth day and the skin healed without slough. Streptomycin was discontinued on the seventh day and penicillin on the fourteenth.

Coughing and diarrhea were noted on November 19. The following day there was intercostal retraction and râles were heard. An x-ray study showed bronchopneumonia and emphysema. A throat culture grew nonhemolytic staphylococci moderately sensitive to Chloromycetin. The child was treated with penicillin, Chloromycetin, oxygen, and water mist. For the next week her condition was poor, with fever, coughing, sternal retraction, and bouts of cyanosis. Eleven days after the onset, clinical recovery seemed complete and specific treatment was discontinued. By December 13, her weight was 6 pounds, 9½ ounces and, after two transfusions totaling 95 c.c., the hemoglobin was restored to 11.5 Gm. by December 16. At 8 weeks the flank bulges were still prominent and there was no evidence of abdominal wall development.

Without guiding precedent, it was reasoned that surgical intervention was necessary if there were to be any development of the abdominal wall such as occurs with large omphaloceles between the first and second stage Gross procedures. This was undertaken on December 17, after first cannulating the left greater saphenous vein with polyethylene tubing through which 75 c.c. of whole blood and 25 c.c. of 5 per cent dextrose in water were given during the procedure. With scopolamine (1/600 grain, preoperatively), open drop ether, and endotracheal nitrous oxide and oxygen anesthesia, the following operation was performed.

A long right paramedian incision was made and extensive adhesions between the viscera and the overlying skin and underlying abdominal musculature were freed. The appendix was at the upper left anterior periphery of the matted intestines which appeared to have performed their own Noble plication. The margin of the muscular and peritoneal defect was freed from the narrow stalk of the mid-gut and protruding gall bladder and uterus, entering into the diminutive peritoneal cavity. Despite the adhesions, the subcutaneous tissue seemed to be undergoing peritonealization. The defect was enlarged to the xiphoid above and the symphysis below between identifiable rectus abdominis muscles. The two halves of the abdominal musculature were approximated to the subcutaneous tissue on either side, employing primarily through-and-through sutures of heavy silk tied over buttons outside the skin (Fig. 3). Of necessity, the muscle edges were well out into the flanks at their midpoints. This obliterated the false herniation between muscle and skin, making the situation similar to that of a large omphalocele after the first stage Gross procedure except for the absence of a peritoneal lining for the skin pouch. The skin edges were closed under slight tension due to the resultant reduction in capacity of the pouch. Again the infant withstood the operation well, although this time of 2 hours and 50 minutes' duration.

Postoperatively, gastric suction was employed and the child was maintained on parenteral fluids for 2 days. Thereafter feedings were well retained. Oxygen was necessary for a short episode of cyanosis the day after surgery. Penicillin and streptomycin were given prophylactically for 3 days. Peristalsis was seen through the skin the first postoperative day and bowel movements were resumed on the third day. Most of the sutures were removed on the tenth day, but the stay sutures were left in place until the fourteenth day. Erythrocin was administered for 6 days for a superficial infection of the incision. Despite this, the incision healed well and there were no further complications. The muscle edges could be felt through the flanks and there was a striking absence of the previous flank bulges of the skin pouch.

The patient was discharged from the hospital on Jan. 5, 1957, weighing 6 pounds, 6½ ounces. Interstitial herniation between the skin and muscle along the middle third of the muscle edge on both sides was noticed about 1 month later. When the child was next seen on June 7, 1957, she weighed 16 pounds and was 25 inches in length. The herniations were larger and it was decided to repair them.

On June 12, at the Fish Memorial Hospital in New Smyrna Beach, Fla., through a short transverse incision in the skin of the right flank, this side of the musculature was reattached along its loose middle third, employing interrupted sutures of fine silk reinforced with stay sutures of heavy silk tied over buttons on the outside. Adhesions were present, but peritonealization of the subcutaneous tissue was more prominent. There were no complications and the child was discharged on the sixth postoperative day. On December 6, 1957, the left side was similarly repaired. The child was discharged on the third postoperative day and her incision healed per primam.

On May 17, 1958, at 18 months of age, development was entirely normal except for the abdomen. She weighed 24 pounds, was 30 inches in height, and was walking and beginning to say words. The abdominal musculature showed modest development despite a slight further recurrence of interstitial herniation along 2 cm. of the muscle edge on both sides. The skin pouch was slack and seemed to move with a measure of freedom from the underlying intestines. Enemas were necessary at regular intervals, apparently due to the child's inability adequately to increase her intra-abdominal pressure.

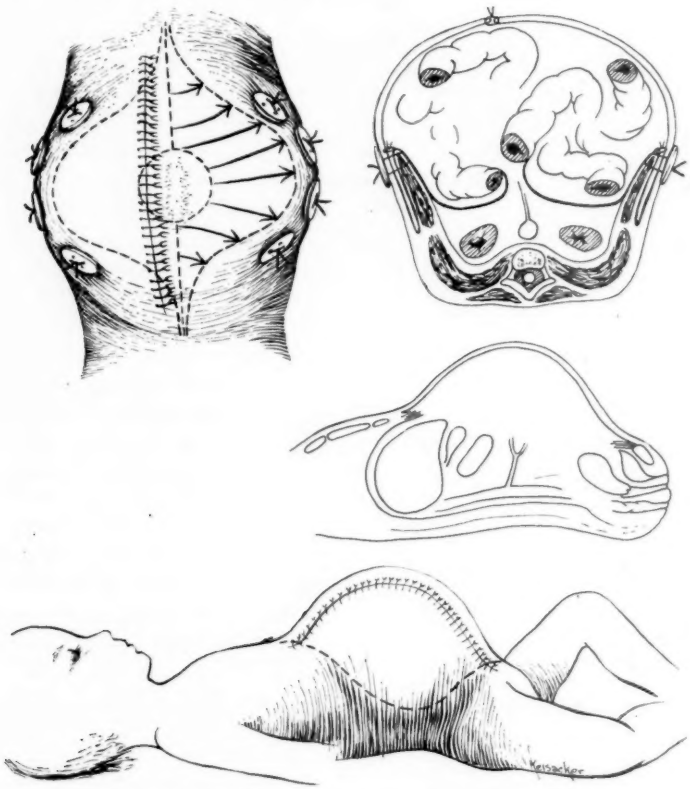

Fig. 3.—Author's solution to the second problem.

When last seen on Dec. 11, 1958, at approximately 26 months of age, the improvement was striking. Marked development of the abdominal wall and cavity without change in the size of the defect had left the pouch slack and the herniated viscera largely reducible. However, the edges of the rectus muscles could still not be approximated across the center of the defect. General development had continued normally with a gain of 3½ inches in height.

DISCUSSION

Covering the exposed abdominal viscera with the widely undermined skin of the abdomen and flanks was the only feasible initial treatment for this

case of gastroschisis with marked disproportion between the size of the eviscerated mass and the capacity of the abdominal cavity.

This proved lifesaving, but left a perplexing condition. Unlike an omphalocele, there was no membranous sac to extend the peritoneal cavity and to transmit a developing tractional force to the musculature. The denuded abdominal musculature, like an iris diaphragm about the narrow stalk of the mid-gut, remained behind the bulk of the abdominal viscera, separating them from the diminutive peritoneal cavity. The force of the skin tended only to collapse further the peritoneal cavity and adhesions might be expected to prevent any spontaneous migration.

It was reasoned that, once the cutaneous envelope had stretched sufficiently to permit a modest reduction in its capacity, the abdominal musculature might be divided into its right and left halves and reattached to the abdominal skin to provide the missing traction. This procedure and the subsequent attempts to correct interstitial herniation disclosed a definite tendency toward endothelization of the subcutaneous tissue which may provide the second function of the missing sac by extending the peritoneum and offsetting the adhesions.

It is hoped that further development of the abdominal wall will eventually permit its complete repair. Staged excision of the skin pouch and lysis of adhesions may be necessary before this can be accomplished. Unless corrected, the thin-walled, pendulous abdomen may create considerable psychic and social problems in later life. The intestinal nonrotation seems compatible with normal existence.

SUMMARY

1. The successful application of skin closure in a case of gastroschisis, with marked disproportion between the size of the eviscerated mass and the capacity of the abdominal cavity, is reported.

2. Due to the absence of a membranous sac, development of the abdominal cavity and wall does not follow unaided as is the case with large omphaloceles following the first stage Gross operation.

3. A procedure is presented for staged obliteration of the subcutaneous space by first suturing the muscles to the subcutaneous tissue. This has resulted in returning the viscera to the abdomen which has increased in size.

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AN EXAMINATION OF CAUSES OF DIFFICULTY FOLLOWING OPERATION FOR HYPERTROPHIC PYLORIC STENOSIS

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THIS report concerns 11 of a group of 218 infants with congenital hypertrophic pyloric stenosis treated at The Johns Hopkins Hospital and the Sinai Hospital of Baltimore during the past 20 years. These 11 children had prolonged hospitalization or troublesome courses, experiencing more vomiting postoperatively than is ordinarily expected. One child succumbed.

Congenital pyloric stenosis must be regarded as a disease in which diagnosis for the most part is not obscure, and therapeutic considerations are familiar. In this country there has been general acceptance of the Fredet-Rammstedt pyloromyotomy as the surgical procedure of choice. Nonoperative therapy with prolonged courses of antispasmodic drugs continues to be favored with varying degrees of enthusiasm by several of the British and continental clinics. Regimens employing drugs have been utilized sporadically in this country in the hope of eliminating operation, but none has retained favor.

A very low mortality is now expected in the treatment of congenital pyloric stenosis. A low threshold of suspicion for the diagnosis, roentgenography when the diagnosis has remained in doubt, the ability to correct water and electrolyte imbalance, standardization of medical therapeutic regimens, and familiarity with what operation has to offer have achieved this happy state. Hospital stays have been reduced to periods of 5 to 8 days following surgery and the incidence of serious postoperative morbidity is extremely low. If the results of treatment are to be improved further, a review of those cases failing to conform to this ideal might prove helpful.

In each of the 218 patients, from which this report is drawn, the diagnosis was confirmed by operation. One hundred and seventy-nine were operated upon at The Johns Hopkins Hospital during the period of 1938 to 1958. Thirty-nine patients were seen and operated upon at the Sinai Hospital. Of the eleven children under consideration, 9 demonstrated a persistent degree of vomiting which lengthened their hospitalization, and 1 succumbed with a bleeding diathesis. In this child and in 5 others blood was demonstrable in the vomitus prior to operation. The remaining 5 patients include 3 who had been operated upon elsewhere but had apparently had inadequate surgery with an unsatisfactory postoperative course, and 2 who had associated gastrointestinal anomalies.

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In the belief that from the experience there can be gained information which will have value through its application to other patients, more detailed presentations are made. The patients are considered under three divisions. The children who demonstrated blood in their vomitus preoperatively comprise a group of 6, which includes the death. A second group includes 3 children who were felt to have had inadequate operations. The children with associated anomalies comprise the third group.

CASE REPORTS

Group I.—Six children with unfavorable postoperative courses, all of whom demonstrated blood in the vomitus or stool preoperatively. One child succumbed with a hemorrhagic diathesis.

CASE 1.—P. O. (J.H.H. A28850). This 2-month-old white male baby was admitted on Feb. 19, 1943, with a history of vomiting for 3 days. The vomiting was projectile in character and on the day preceding admission the patient vomited some brownish material and passed a very dark stool.

The abdomen was soft but one could not be sure that a tumor was palpable. Stool obtained from the rectum was found to be guaiac positive.

The child persisted in vomiting small amounts, although a roentgenogram revealed no obstruction in the stomach or duodenum. Eight days following this, however, a characteristic tumor was palpable. A film taken on March 5, 1943, was thought to indicate pyloric obstruction, and on that day operation was undertaken. A typical pyloric tumor was found and a Fredet-Rammstedt operation carried out.

The child vomited intermittently during the first 6 days postoperatively. He was finally discharged on the twenty-third of March, 18 days postoperatively, at which time he was gaining weight and feeding satisfactorily.

CASE 2.—J. C. (J.H.H. A30456). This 4-month-old child was admitted on June 7, 1943, after persistent projectile vomiting for several weeks. The child had started to vomit during the first 2 weeks of life and continued to do this once or twice daily in spite of repeated formula changes.

On the day following admission, the child vomited only three times and took fluids fairly well. Radiographic study showed pyloric stenosis. Following this study, the child vomited copiously. The vomitus was filled with barium, but admixed with this was dark brown guaiac-positive material. This recurred for 2 more days.

After 7 days in the hospital during which very little progress was made in improving the child's condition, and during which time he repeatedly vomited guaiac-positive material without a fall in hemoglobin, he was operated upon.

A typical Fredet-Rammstedt procedure for pyloric hypertrophy was carried out uneventfully, but for the first 5 days postoperatively he continued to vomit small quantities in ever-decreasing amounts. He was discharged on the thirteenth postoperative day in good condition, gaining weight, and taking a normal diet easily without vomiting.

CASE 3.—W. B. (S.H. 103283). This 2-week-old child was admitted on May 3, 1953, with a history of projectile vomiting for 5 days.

Five days prior to admission the child had begun to vomit in ever-increasing amounts. The vomitus never contained bile but, prior to admission, was observed to contain dark brown material described as old blood.

Examination on admission revealed a palpable tumor. The hemoglobin value was 22 Gm. per cent.

A Fredet-Rammstedt procedure for typical stenosis was carried out on May 6, 1953. For the first 2½ days postoperatively the child had a very stormy course. Numerous, repeated episodes of gasping, spasmodic twitching, and disturbing convulsive movements occurred.

These required intense, specific therapy, directed to correction of electrolyte imbalance. During the ensuing 2 days he fed poorly. He then adjusted rapidly. He was discharged 9 days after operation. The hemoglobin was noted to have fallen to 9.5 Gm. per cent prior to his discharge.

CASE 4.—D. C. D. (J.H.H. B41383). This 16-day-old male was admitted on May 31, 1957, with a history of vomiting for one week, assumed to be due to congenital pyloric stenosis.

For a week prior to admission the child vomited many feedings from minutes to hours after feeding. The vomitus never contained bile or blood.

Examination was essentially unremarkable except for the abdomen where there was a suggestion of gastric peristaltic waves. A fairly well-defined olive tumor was palpable in the right upper quadrant. The blood studies were normal, showing adequate platelets. A barium swallow showed pyloric obstruction. On the second day of admission the child vomited small amounts of guaiac-positive material two times.

On June 4, 1957, the child was taken to the operating room where a typical tumor was found and a Fredet-Rammstedt operation was done. A small duodenal opening was recognized and repaired. An estimated 40 c.c. of blood loss was replaced during operation. The patient did fairly well during the first postoperative day and was kept on gastric suction because of the duodenal entry. One day after the operation the child vomited some blood. He was given a transfusion, since his hematocrit was 17, and on the fourth postoperative day the hematocrit was 36. On the third day the gastric tube was removed. The child had a bowel movement. He vomited guaiac-positive material that day.

Dressings were subsequently removed and a localized hematoma was detected. On the fifth postoperative day, this hematoma decreased in size but the area of hemorrhaging spread across the abdomen. Again the child vomited guaiac-positive material and this increased during the next day. On the seventh postoperative day, it was noted that there was difficulty in stopping bleeding after a venepuncture. The prothrombin time was found to be 57 seconds (less than 20 per cent of normal). The child was given 2½ mg. of Hykinone intramuscularly and 5 mg. of vitamin K oxide intravenously. It was noted that some generalized edema which had begun on the fifth, sixth, and seventh postoperative days seemed to be progressing. The total serum proteins were 3.2, the A-G ratio 1.9/1.3, and it was felt that the edema was on the basis of low serum proteins, although it was not understood why they were so low. A subsequent urine specimen showed a 4+ albumin. This had not been present in the original urine specimens.

The child continued to have yellow, pasty stools. He died on June 11, 1957, 7 days after operation.

At postmortem examination, a massive dissecting hematoma was found in the retroperitoneal space on the right side, well into the pelvis, with a large hematoma under the operative site. The duodenal opening was closed. There were no ulcerations. The pyloric canal was patent.

CASE 5.—B. S. (S.H. 157120). This 1-week-old child was admitted May 10, 1958, with a history of vomiting for 4 days.

On the fourth day of life, the child started to vomit almost every feeding; the vomiting being projectile in character and occurring immediately after feeding. On the day prior to admission it became dark in color and was positive to chemical tests for blood.

Physical examination on admission revealed the child to be well developed, well nourished. No abdominal masses were felt. It was thought that he might well have a gastric lesion and that a peptic ulcer or esophagitis must be considered. The day following admission, a pyloric tumor was palpated.

On May 15, 1958, a Fredet-Rammstedt procedure was carried out for a rather small pyloric tumor. On the day after operation the child vomited coffee-ground material four times. He continued to vomit in small amounts and was started on tincture of belladonna 3 days after operation. By June 2, more than 2 weeks after operation, he still vomited intermittently to the extent that it was necessary to supplement his oral intake by clysis. Gastric

lavage revealed no notable amount of retention and no obstruction to stomach or bowel was found on radiologic examination. Despite the intermittent use of Thorazine, thickened feedings, and formula changes, the child continued to vomit. Diligent search failed to reveal a focus of infection.

Five weeks after operation it was noted that the child still continued to spit up slightly and to vomit 2 or 3 times a day, but that he was beginning to gain some weight. The vomiting gradually diminished, and he was eventually discharged on July 3, weighing 7 pounds 15 ounces, which represented a one pound weight gain over his admission weight. It is significant, however, that this gain in weight began only on the ninth of June which was 3½ weeks following his operation. The child has remained well since.

CASE 6.—K. J. (J.H.H. B56928). This 1-month-old white male child was admitted Oct. 18, 1958, with the story of 4 days of vomiting. Four days prior to admission he vomited his formula and then continued to vomit every feeding during the day. One night prior to admission the vomitus became brown in color. On the morning of admission, he produced a bowel movement which was dry and green.

On admission to the hospital the child appeared to be quite well. Peristaltic waves were noted across the abdomen, vomiting was projectile, and it was thought that a pyloric tumor was felt. On the following day he passed a dark black stool which was guaiac positive, and on the day following this the pyloric tumor was unquestionable.

This child was operated upon on the twenty-third of October at which time a typical, large, pyloric tumor was found. A Fredet-Rammstedt procedure was carried out. The submucosa was edematous. He was begun on 6 drops of belladonna daily postoperatively. Feedings were begun the next day. Belladonna was continued through the first 3 days postoperatively, on the premise that the child had either duodenitis or gastritis to account for the blood in his vomitus and stool. His postoperative course was unmarked by complication but for the first 3 days he vomited at least once or twice daily. He was discharged well on the tenth postoperative day, gaining weight saisfactorily.

Review: Six case histories are presented. These children all demonstrated blood in vomitus or stool prior to operation for congenital hypertrophic pyloric stenosis. In one instance, bleeding persisted postoperatively and a prolonged prothrombin time was demonstrated on the seventh postoperative day. This child died (Case 4). Another child vomited persistently for 5 weeks following operation (Case 5). One infant experienced serious seizure-like episodes for 2 days following operation (Case 3). In the other 3 cases (1, 2, and 6) the postoperative course was marred by more vomiting than is usually anticipated.

Discussion: If a less than ideal course following pyloromyotomy can be attributed to conditions complicating the simple congenital hypertrophic pyloric stenosis, an indication of the nature of the complication should prove helpful in the management of the patient. There were 10 infants who showed blood in their vomitus or stool prior to operation in the total number of 218 cases surveyed (4.6 per cent). While 4 of these infants experienced no untoward event, the 6 children who bled and experienced less satisfactory clinical courses have been described in detail above.

In no instance of the 6 was there a great quantity of blood vomited preoperatively. No correlation was possible on the basis of age, duration, force, or amount of vomiting which would afford a clue as to the importance of the process causing the bleeding.

The classical writings of Ladd and his colleagues[9] in 1946 make mention of the occasional presence of blood in the vomitus of infants with congenital

pyloric stenosis. Donovan[1] alludes to the fact that the vomitus may have mucus, bright blood, or coffee-ground material presumed to be due to gastritis or to the rupture of a vessel in the gastric mucosa.

The review of 320 instances of pyloric stenosis presented by Wood and Smellie,[18] in 1951, mentions that in 27 of the 320 cases there was blood in the vomitus. Although there were 5 deaths in the series and 12 patients had severe postoperative vomiting, there is no comment made with regard to any relationship between these latter 17 and the 27 originally presenting with blood in the vomitus.

It is of interest that the French authors had concerned themselves with this possible relationship from an earlier date. Ribadeau-Dumas, Chabrun, and Loewe-Lyon[14] discussed, in 1937, a "hemorrhagic form of hypertrophic pyloric stenosis in the newborn." They mentioned that, in the clinical picture of pyloric stenosis, hematemesis is an inconstant and incidental symptom. However, they present a case report of an infant in whom the hematemesis was abundant, early, and repetitive. This was a full-term child who began to vomit on its fourth or fifth day of life. On the twenty-fourth day of life he had a classical pyloromyotomy. The child recovered well from the operation, but had large hematemesis again on his thirty-ninth, fifty-third, and fifty-sixth days of life. The child finally ceased his vomiting and recovered. The authors conjecture on three possible causes for this: The first, melena of the newborn, did not seem to apply. The second, that the child might have a hemorrhagic diathesia, was likewise not proved. They discuss then pyloric stenosis and a peptic ulcer. The authors mention that such ulcerations are notoriously hard for the surgeon to see and that what they refer to as the "hemorrhage of stasis" in adults is independent of the cause of the stasis. It was their conclusion that hemorrhage must not interfere with the diagnosis of congenital pyloric stenosis and surgical intervention.

Josserand, Giroud, and Gouteyron[7] amplified this experience in the French literature. In 7 of their patients, blood made its appearance in the vomitus during the pre- or postoperative course. They add three reports of others and divide these 10 instances into two categories. The first group of 5 of their own patients are children in whom the appearance of blood was small in quantity and apparently not significant in altering the clinical course. These might correspond to our 4 instances which are not considered of consequence The second category is so called "hemorrhagic form"; and they add to their 2 patients the one previously presented by Ribadeau-Dumas and 2 cases of Schneegans. One of the authors' patients had large hematemesis and although transfusion was not needed, the child was hospitalized for 3 months. A second child had several large hemorrhages, required transfusion, and spent 22 days in the hospital postoperatively. Both of 2 patients of Schneegans referred to required transfusions. The authors feel, with the previous authors, that the bleeding tendency is secondary to stasis and gastritis. They conclude that minimal, late appearance of blood, as in their first category, has neither therapeutic nor prognostic

significance and they do not believe that this type of phenomenon merits consideration as a "hemorrhagic form." They apparently choose to overlook the fact that one of these 5 "mild" cases died preoperatively, while the other 4 remained in the hospital for 9, 17, 29, and 26 days!

Our experience would tend to justify the view that the appearance of blood in the vomitus or stool of a child with congenital hypertrophic pyloric stenosis should not be casually dismissed. It would appear that in such patients there is a good likelihood that persistent vomiting or failure to feed properly may ensue upon operation. Indeed, the sign may be a direct warning, as in one instance, of a coagulation disorder. We find little in the experience of others to contradict this view.

There is much that is attractive in the premise that the appearance of blood in the vomitus of these infants results from gastritis, erosion, or ulceration. The obstruction in itself may be somehow causally involved in this secondary condition.

In 1951, Dragstedt and his colleagues[3] demonstrated experimentally in dogs by antral transplants to the colon that a Heidenhain pouch secreted profusely under stimulation of such a transplant. Antral pressure appeared to stimulate gastric secretion. Dragstedt[2] conceived of gastric ulcer as being due to dysfunction or hyperfunction of the antrum resulting in an excessive and prolonged liberation of gastrin. In 1955, he and his colleagues[15] produced experimental pyloric obstruction in dogs, leading to persistent hypersecretion of gastric juice of humoral origin. In 6 dogs, one gastric ulcer was thus produced and hypertrophy of the gastric mucosa occurred in all. It was felt that this might account for gastric ulcer in those patients with pyloric obstructive lesions. There is direct and indirect substantiation of these observations in clinical experience.

Nielsen and Roelsgaard[12] felt that they were able to demonstrate radiologically a higher incidence of peptic ulcer in adults who had been treated for congenital pyloric stenosis than in a control group. In another communication, Nielsen discusses 95 individuals over 25 years of age who had had pyloric stenosis in infancy.[11] A follow-up questionnaire revealed that 28 per cent of these people as adults had developed frank ulcer or severe dyspeptic symptoms versus 12 per cent in a control group.

Hertz presented a series of studies, clinical and pathological, concerned with congenital pyloric stenosis of the newborn in Copenhagen in 1916. Several instances of hematemesis of varying degree were noted among his patients. Postmortem examination of the stomach in these children revealed multiple erosions in the gastric mucosa.[5]

In 1925, Kleinschmidt[8] of the University Pediatric Clinic in Hamburg presented an instance of bleeding ulcer in a newborn with congenital hypertrophic pyloric stenosis.

Thus, there appears to be a physiological mechanism which can be demonstrated experimentally and, perhaps echoed in clinicopathological experience, whereby gastritis, erosion, or ulceration may occur in these infants.

Hollander cites an infant who succumbed postoperatively to hemorrhage from a duodenal ulcer. It is noteworthy that this may occur, however difficult to explain.[6]

The esophagus might provide another source for the blood in the vomitus of these infants. The autopsy protocols at The Johns Hopkins Hospital yield 14 instances of postmortem examination in infants succumbing to congenital pyloric stenosis between the years of 1914 and 1936. In 9 of these, no significant comments are made with regard to the esophageal or gastric mucosa—or such comment as is made describes no abnormality. In the last 5 patients, however, examined between May of 1927 and January of 1936, esophageal mucosal changes were noted in every instance. These ranged from excessive thinning of the wall of the esophagus through superficial esophageal erosion, roughening and denuding of the esophageal epithelium, ulcerative esophagitis, and thin new epithelization of areas of the esophagus apparently healing over previously ulcerated areas. Two of these children had been subjected to repeated lavage. It is entirely conceivable that the esophageal damage was attendant upon the abrasion of the gastric tube. In the remaining 3 cases there was no known trauma. It would seem reasonable to infer, therefore, that trauma to the esophageal wall induced by vomiting or by the repeated passage of the gastric tube may provide trauma to the esophagus, causing it to bleed.

In our own patients with bleeding in whom radiographic examination was carried out preoperatively, no lesion was noted which might afford a clue as to the source for the blood. This, however, is not to be considered remarkable. When one takes cognizance of the difficulty in demonstration of shallow juvenile peptic ulceration under optimal circumstances, and the superimposed hindrance of the pyloric obstruction.

Without further elucidation of specific pathology, certain conclusions seem warranted: (1) the child who vomits blood even in microscopic quantity preoperatively merits careful attention as a possible candidate for a less favorable postoperative course, (2) this bleeding may be the first overt indication of a blood coagulation disturbance, and (3) there may be severe gastritis or a degree of peptic ulceration accompanying the pyloric stenosis.

Certainly, in every instance, a complete survey of the bleeding and clotting mechanism is indicated. If postoperatively, vomiting of any moment persists beyond the second day, we have felt justified in counselling a regimen which includes antacid-antispasmodic drugs and small divided feedings. While this may obtund the drama of the usual rapid, brilliant recovery, we have felt that it served to diminish the chance of serious setback.

Group II.—Three instances of persistent postoperative vomiting apparently on the basis of inadequate lysis of the pyloric tumor.

CASE 7.—R. T. (J.H.H. A77756). This 3½-month-old white male was first admitted to The Johns Hopkins Hospital on April 20, 1950. He had been previously hospitalized and operated upon for hypertrophic pyloric stenosis. At 2 weeks of age, the child had begun to vomit material, not stained with bile, in a projectile fashion. At the age of 5 weeks, he

had been admitted to a hospital acutely ill and dehydrated and, after a week of trial on nonoperative therapy, a Fredet-Rammstedt procedure was carried out for a large pyloric tumor. Postoperatively the patient continued to vomit and failed to gain weight. This continued even after discharge from the hospital and the child was admitted to The Johns Hopkins Hospital for consideration of this problem. The original impression was that the child had been inadequately operated upon. There was a pyloric tumor palpable.

Ten days of therapy with thickened feedings were tried without effect and finally on April 30, 1950, the child was again explored. There seemed to be scarring in the region of the gastroduodenal junction and a definite obstruction in this region. The pyloric tumor was quite large and again a pyloromyotomy was carried out. The child had a completely benign postoperative course. He vomited slightly 2 days postoperatively and was discharged on his tenth postoperative day gaining weight very rapidly.

CASE 8.—S. C. (J.H.H. B960). This 7-week-old child was admitted with the chief complaint of vomiting on March 20, 1953. On March 2, 1953, the child had been hospitalized elsewhere for vomiting with the diagnosis of hypertrophic pyloric stenosis. Pyloromyotomy was carried out on March 2, 1953. The child was discharged from the hospital 8 days following this. After discharge the child continued to vomit intermittently every other feeding. No bile was found in the vomitus, but on several occasions the child vomited brownish material which tested positive for blood.

Examination at time of transfer to The Johns Hopkins Hospital was essentially unremarkable. Barium studies confirmed the persistence of obstruction and, while in the hospital, the child had several episodes of projectile vomiting. On March 27, an operation was carried out at The Johns Hopkins Hospital. It was felt that the division of the pyloric tumor had been inadequate at its proximal end over the distance of perhaps one inch. This area was incised. The child's postoperative course was completely uneventful and she was discharged 8 days postoperatively.

CASE 9.—M. B. (J.H.H. B16476). This 16-day-old child was transferred to The Johns Hopkins Hospital on Dec. 25, 1954. The child had been doing well until 8 days after birth when projectile vomiting began. No bile was noted in the vomitus. A barium meal revealed no evidence of pyloric tumor. However, on the evening of December 20, the patient was operated upon for pyloric obstruction. The pylorus is said to have been white and to have a contraction of its mid-portion. In splitting this, the duodenum was opened. The baby continued to vomit after operation. There was fresh blood in the vomitus during the first day postoperatively, and old, changed blood thereafter. The hemoglobin did not fall.

At the time of transfer to The Johns Hopkins Hospital the stools contained blood, and the child persisted in vomiting. The child was kept on frequent small feedings and tincture of belladonna. Upper gastrointestinal series revealed gastric retention and a narrowing of the antrum and pylorus.

On the fourth of February, an upper respiratory infection resulted in a recurrence of the vomiting which was slowly beginning to subside by this time. Her feedings were gradually resumed until the fourteenth of February at which time they had returned to the normal volume of 60 c.c. Further radiologic studies on March 25 still showed some gastric dilatation and considerable time lag before the barium started through the pylorus, but it had improved over the previous set of films.

The patient was discharged on April 4, 1955. A follow-up gastrointestinal series on June 20, 1955, showed no significant pyloric narrowing.

Review: Three patients are presented in whom pyloromyotomy was not curative, despite demonstration of typical lesion at operation. In 2 instances (Cases 7 and 8), second operations were carried out and pyloric tumors were found. Pyloromyotomy gave prompt relief. In the third patient (Case 9), the

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duodenum had been entered and there was a persistent appearance of blood in the vomitus and stool for several days postoperatively. During 3 months in the hospital, the obstruction yielded.

Discussion: Although Robertson[16] is responsible for the statement that one need not be concerned over leaving a few fibers at the duodenal end of the tumor, other authors have taken issue with this view. Certainly exquisite judgment must be brought to bear if one is to commit himself to less than complete lysis. Patient 7 (R. T.) seems quite clearly to fall into this category, with a pyloric tumor being revealed at second operation and obstruction distally.

In Patient 8 (S. C.) significant obstruction was found over the proximal end of the old tumor. The operator felt that the tumor at this end might still be circumferential. Actually, obstruction may ensue if the incision is too short proximally, even if hypertrophy does not girdle the antrum. Fredet[4] points out that if the proximal end is permitted to remain rigid, sliding of the mucous membrane upon it may cause obstruction. Further, one may conjecture as to the possibility that further hypertrophy may develop if obstruction remains.

It is apparent that while some room for difference of opinion may exist, nothing short of complete lysis will permit the conclusion that the patient's chance for cure has not been compromised.

Group III.—Two cases of congenital hypertrophic pyloric stenosis associated with gastrointestinal anomalies.

CASE 10.—A. D. (S.H. 122844). This 3½-week-old child was admitted on March 30, 1955, with the chief complaint of vomiting since the fourth day of life. On the fourth day of life the baby had started to vomit most of its bottle; the feeding "gushed out." Conservative measures served only to control the vomiting for a few days, and atropine and belladonna were prescribed on an outpatient basis, but the baby continued to vomit 15 to 20 minutes after feeding.

On admission, the baby was started on atropine after each feeding and on the day after admission it vomited only twice. There was a definite impression among observers that there was some definite hyperperistalsis, and the child began slowly to vomit once or twice daily.

By April 13, the baby had sustained a 13-ounce weight loss and had forceful emesis. It was felt by some that a pyloric tumor could be palpated, and others doubted this. Accordingly, on April 14, 1955, an x-ray study was made which revealed chalasia of the esophagus and a pyloric string sign. Propping the child up in its crib and dividing its feedings had only slight effect upon the vomiting and operation was recommended for the suspected pyloric stenosis. As operation was scheduled the child began to have episodes of convulsions. These persisted for several days intermittently, then gradually subsided. No correlation with abnormal serum chemistries was discerned.

On May 4, 1955, the child was explored. At operation a very large stomach with a rather typical pyloric olive-shaped tumor was found. A classical Fredet-Rammstedt procedure was carried out. The child on the whole did well postoperatively, remained afebrile, but, because of the degree of distention, was kept on suction for several days. By the eighth of May the child was retaining all of its feedings without vomiting, although gastric waves could be seen intermittently. Suddenly, however, on May 10, the child began to vomit again and developed a distended abdomen. X-ray of the abdomen on the eleventh of May revealed a fairly large gastric bubble and no other abnormality. The child was thought to be vomiting because of its chalasia which was still visible and it was put on small feedings. By the thirteenth of May, it began to gain weight well and was discharged on May 17, 13 days after operation, at which time the child had stopped vomiting for 3 days, was gaining weight satisfactorily, and was considered to be getting well.

CASE 11.—K. C. (S.H. 152609).* This 6-week-old white female was admitted on Oct. 18, 1957, with a history of vomiting for 9 days. Beginning to vomit 9 days prior to admission, this child had retained only 13 ounces of 45 ounces offered during the 4 days preceding admission. Despite treatment with antispasmodics, it was felt that the vomiting was increasing in severity although it did not have a projectile character. No blood or bile was noted in the vomitus.

Examination on admission revealed a typical pyloric tumor. Three days were taken to correct the child's dehydration and alkalosis, and, on October 29, the child was operated upon. The tumor was split in the usual manner. A small opening was made into the duodenal mucosa which was repaired by suture and omentum.

The child gradually became more distended and vomited several times postoperatively. Three days postoperatively, Oct. 23, 1957, the vomiting was noted to be bile stained. A roentgenogram of the abdomen revealed numerous air fluid levels in the lower bowel and it was felt that the child might have ileal obstruction, for reasons which remained obscure. Accordingly, 4 days following pyloromyotomy, Oct. 24, 1957, the child was submitted to laparotomy. A congenital band across the ileum was lysed. It was felt that this was the cause of the child's obstruction.

Postoperatively the child did very well. Three days after operation it was feeding well and it was discharged on Oct. 30, 1957, 6 days following laparotomy, eating, passing feces, and gaining weight very satisfactorily.

Discussion: The coincidence of congenital hypertrophic pyloric stenosis and chalasia is unusual. Little to this point can be elicited from the literature, but the reviews of many hundreds of cases of congenital pyloric stenosis fail to allude to it. Neuhauser and Berenberg[10] commented in their original report on 12 patients with chalasia that only one child had another anomaly. However, although it does not relate specifically to the point, Robins and Jankelson[17] found that 88 of their 103 adults with cardioesophageal relaxation had other significant illness.

Of our experience with this combination of diseases, it can only be stated that the diagnosis was thereby confused. Once pyloromyotomy was carried out, some 10 days transpired before vomiting was completely stopped and satisfactory weight gain began. We are inclined to attribute this to the presence of the chalasia. Although Neuhauser and Berenberg, in their original communication, state that these infants become well almost immediately, our own experience has been rather less dramatic. We have not felt that periods ranging from 2 weeks to 2 months were unusually long to permit this relaxation to correct itself. Palmer[13] mentions that it takes 2 to 5 months to develop spontaneously an adequate closing mechanism. In our patient, the sequence of events seemed to parallel closely those to which we are accustomed in the handling of the infant with chalasia.

The second instance of associated anomaly again demonstrates the danger of possible oversight. Inadequate attention to the possibility of intestinal obstruction or a dismissal of the vomiting as "expected" might have eventuated fatally.

While coexistence of these anomalies is rare, it behooves one to bear in mind that as one diagnosis does not exclude another, neither may one's threshold of suspicion be raised after diagnosing and treating congenital pyloric stenosis.

*This patient of Dr. Howard Kern is discussed in detail by Dr. Kern in a forthcoming report in *The Sinai Hospital Journal.*

CONCLUSION

The results of surgical treatment of congenital hypertrophic pyloric stenosis are most gratifying. In a small group of patients, however, an opportunity is afforded for further improvement.

It would appear that the child who experiences hematemesis preoperatively has somewhat reduced chances for a completely favorable course following pyloromyotomy. Prolonged vomiting postoperatively, feeding difficulty, or recurrent bleeding are more likely to occur in this group than in patients who have not vomited blood. We have been sufficiently impressed with this to recommend a complete survey of the bleeding and clotting mechanism preoperatively in any infant with hematemesis. Following operation, if any vomiting persists beyond the second day, we have felt that a regimen of very small divided feedings and antacid-antispasmodic drugs should be instituted.

The patients in whom lysis of the tumor has been inadequate remain as another small but troublesome group. Secondary operation promptly instituted affords the opportunity for rapid recovery.

In the rare child with a second and unsuspected congenital anomaly, a lower threshold of suspicion for this possibility may preclude serious complication.

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Editorial

Conducted by I. S. Ravdin, M.D., and J. Garrott Allen, M.D.

Required Student Research

Dana Atchley has written a thought-provoking article on Medical Education in which he says: "In order to ensure the highest quality of medical practice, our first and foremost duty is to graduate medical scientists." (In broad terms, a scientist is one who with a disciplined intellect studies natural phenomena.) He then goes on to say, "If the thesis be accepted that a medical student should in the course of his training become a scientist, we must face the very difficult problem of implementing this decision. Probably there is no more fundamental requirement for the attainment of this goal than an atmosphere of research."[1]

Can research be made an integral and required part of the medical school curriculum? This depends on the school, the faculty, and the student.

So far as the school is concerned, the adoption of a required program may be a matter of basic philosophy. Expansion of neither classroom nor laboratory space is necessary if the faculty are actively engaged in research and facilities for their work are adequate. An allocation of no more than one hundred dollars will usually cover direct expenses of a student project. The essential requirement is time and this must be provided by an adjusted curriculum.

Twenty-five per cent of American medical schools now require a research or library project for graduation. An additional 11 per cent of schools require the submission of an essay or thesis, not usually based on original research.[2] Dean Lippard in his appraisal of the required thesis at Yale wrote: "It is our contention that opportunity to explore critically the literature in a limited field, to learn something about the experimental method, to bring an investigation to a conclusion and write a report, to know the strengths and limitations of biological research, to have curiosity stimulated, and to work intimately with the faculty enhance the competence of a physician and make him a better citizen of the medical world."[4]

To assure the support of student research by the school, it is necessary that those in authority be convinced that the student destined to be a practitioner will profit quite as much from this program as the student who will follow an academic career.

What about the faculty? Department heads are nearly all in favor of student research, at least as an elective.[2] From a personal experience of more than 10 years with a required student program, I have no illusions about the

difficulties and frustrations. If there is to be maximum benefit, the program becomes a time-consuming responsibility to the faculty member. He should carry no more than three student projects at a time and preferably only one or two. The obvious implication is that such a program, to function efficiently, requires a high faculty to student ratio. It is also obvious that, for a number of reasons, a full-time faculty can more easily adapt to this program than can a part-time faculty.

The intimate relationship and mutual respect that develops between faculty advisor and student, in their joint attack on a research problem, is one of the principal dividends of the program. Certainly, student research does not always result in the establishment of a new fact; but never has an exploration with the student failed to lead to the place where these facts may be found. What is more important, it has given the faculty member the opportunity to impart to the student the essence of the Darwinian revolution: "The right of an individual to trust his own eyes, and form his own judgments, tell the world his belief, and have the matter cleared by open trial and honest evidence."[5]

What does the graduate think of student research? Ebbert canvassed graduates from a school with a required student research program and found that 98 per cent looked back upon it as a valuable experience.[3] Sixty-one per cent were in favor of required research. It is of further interest that 65 per cent of these graduates who favored student research are in private practice. Two-thirds of those now in the full-time academic medicine believe that the thesis project influenced them in the selection of their careers. Eighty-four per cent of the graduates thought their thesis project had helped them to judge the work of the others with more discrimination, which is so important in a dynamic field where self-education must continue throughout one's professional life.

This editorial expresses enthusiasm for research as part of the medical curriculum. Required research has worked well in a school with a medium-sized student body and a relatively large full-time faculty. Obviously, such a program is not immediately adaptable to many schools. However, if required research is not the answer for all schools, it is imperative that another plan be evolved to ensure an environment of research, practical for the administration and magnetic for the faculty and the student.

If it is agreed that the ultimate aim of physicians is the prevention of disease and the indefinite prolongation of life, the problem is clearly worthy of solution by the best brains our society can produce. But unless we provide the means through a carefully directed research program for the maximum development of our talented students, it is inevitable that progress toward this goal will be seriously delayed. If there are any who fear submersion of the *art* of medicine by the *science*, let them remember that to practice scientific medicine one does not have to give up the ideal of compassion for human suffering. Progress in medical care demands a scientific approach to the patient's problem, whether it be at the bedside or in the research laboratory.

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Recent Advances in Surgery

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RECENT DEVELOPMENTS IN COLON SURGERY

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A REVIEW of the articles which have shaped current thought on surgery of the colon during the past 5 years has made it apparent how much our day-to-day thoughts are constantly undergoing change, and how many of the ideas now accepted without question are either quite recent in origin or else have only recently been re-emphasized. Other reviewers[35, 45] have also noted the progress of recent years.

COLON INJURIES

Injuries to the colon are fortunately much less frequent in civilian than in military life, but anyone surveying the experience of a hospital with a large emergency practice knows that colon injuries are still very much with us. One such review by Tucker and Fey[44] analyzed 42 cases of perforating injuries of the colon and rectum with a mortality of only 14.3 per cent. The majority were gunshot injuries, as one might anticipate. The review was particularly concerned with the results of primary suture of these wounds. There were no deaths in the 17 cases so treated and the only complication was a single wound abscess. The average period of disability was 11.8 days when primary suture was utilized, 31 days when primary resection and anastomosis were utilized, and 58.2 days when two operative procedures were required. Primary closure was usually employed in wounds not over 2 inches in length, and usually in those who received treatment within 6 hours after injury. The authors concluded that primary closure in selected cases is not only safe but is the preferred procedure. The lowered mortality and morbidity of this form of therapy for wounds of the colon were attributed to the extensive use of antibiotics.

ANTIBIOTICS IN COLON SURGERY

Since antibiotics have been so widely used in colon surgery, it would be desirable to have some specific indication of their role rather than the generalizations that have been made by those who either do or do not advocate

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the use of antibiotics in colon surgery. Cohn and Rives[10] studied this experimentally, since a clinical demonstration of the role of antibiotics was thought to be dependent on too many different factors to permit its proper evaluation. An experimental operative procedure which put a colon anastomosis under extreme stress was utilized as a means of determining whether antibiotics had any real protective value in colon surgery. After an anastomosis was made in the colon, the blood supply to one side of the anastomosis was divided. Control animals received no further therapy while treated animals received antibiotics delivered into the lumen of the colon by means of a plastic tube inserted into the bowel at the time of operation. Control animals died while most of the treated animals survived, demonstrating that antibiotics administered in this fashion can exert a protective action upon a colon anastomosis. The study was divided into three groups of experiments, in the first of which no preoperative preparation of any kind was used, in the second, only preoperative mechanical cleansing was used, and, in the third, both preoperative mechanical cleansing and preoperative intestinal antisepsis were used. While each form of preoperative preparation was beneficial, the maximum protection was afforded by combining preoperative mechanical cleansing, preoperative intestinal antisepsis, operative intracolonic administration of antibiotic powder, and postoperative intraluminal antibiotic administration. Thus, experimental evidence has been found for the beneficial use of antibiotics in colon surgery.

On the basis of this work, a triphasic clinical study has been under way in Charity Hospital in New Orleans since July, 1955.[7] All patients prepared for colon surgery on the Louisiana State University Surgical Service are prepared with a combination of tetracycline and neomycin, as well as with the usual means of mechanical cleansing. Whenever the colon is opened in any operative procedure, a powder containing the same two antibiotics is placed in the lumen of the colon. A plastic tube is also inserted into the bowel and exteriorized, and through this tube a combination of the same antibiotics is injected three times a day for 5 days postoperatively. Since this program was instituted, 275 patients have been included in various portions of this study. There are 52 patients who received all three forms of therapy as originally outlined in the experimental work. Those prepared with the combination were subjected to all kinds of operations, the largest group being the 107 who were subjected to some type of colonic procedure with a primary anastomosis. This clinical investigation is still under way, but the impression at the present time is that the triphasic program adds to the safety of colon surgery and that patients receiving this kind of antibiotic protection have fared better than comparable cases where this form of antibiotic therapy was not practiced.

Cohn and Longacre[9] have conducted a 4-year study of intestinal antiseptics, comparing the reduction of the bacterial flora obtained with different agents studied under standardized conditions. They divided the 30 intestinal antiseptics into three categories. Those not recommended include the broad

spectrum antibiotics, the sulfonamides, and some of the antistaphylococcal agents. These agents do not satisfactorily control the bacterial flora of the bowel and many of them produce so many side reactions as to be undesirable on this basis alone. In the intermediate group are three agents, one of which, neomycin, is perhaps the most widely used single agent for this purpose. The recommended drugs are divided into those recommended only for special purposes, and those recommended for general use. This latter category includes combinations of neomycin with amphotericin, bacitracin, nystatin, polymyxin B, Sulfathalidine, or thiostrepton, and the only single drug to be so recommended—kanamycin.

One problem which some attribute to antibiotics has not been fully explained because of the lack of an experimentally produced form of the disease for study purposes. Two recent articles[32, 42] report experimental methods for the production of pseudomembranous enteritis. One study in dogs showed that all of the following factors operating simultaneously were necessary for the production of this state: a temporary low ileal obstruction, the intestinal instillation of broad spectrum antibiotics, the intestinal instillation of an antibiotic-resistant staphylococcus, the systemic administration of penicillin and streptomycin, and the administration of a bowel relaxant. This combination of factors produced a mucosal lesion in 30 per cent of the animals so treated. The other study showed that the disease could be created in chinchillas by the oral administration of broad spectrum antibiotics for 1 to 3 weeks with the administration of a suspension of pure culture of staphylococci beginning on the sixth day of antibiotic administration. Thus, reproduction of the disease requires prolonged antibiotic administration combined with massive amounts of pure bacterial cultures which would provide intra-intestinal conditions which are ideal for bacterial growth. The infrequency with which such relatively ideal conditions exist in patients might explain the relative infrequency of this problem in patients who are not carried for prolonged periods on intestinal antibiotics.

DIVERTICULITIS

The advent of satisfactory intestinal antiseptics and the widespread use of antibiotics have produced a change in the approach to diverticulitis. Waugh and Walt[50] describe their experiences with diverticulitis from 1945 to 1954 and noted the increasing frequency with which one-stage procedures were utilized in their own institution. The low mortality and morbidity, as well as the shorter period of hospitalization, made this a safe and recommended procedure under certain circumstances. While about 80 per cent of the cases remain medical problems, an early decision for surgery should be considered in the presence of: (1) recurring attacks of abdominal pain and fever despite good medical management, (2) episodes suggestive of subacute obstruction, (3) evidence of one or more subacute perforations with localized peritonitis, (4) the association of more than minor urinary symptoms, (5) the presence of a mass that does not resolve rapidly with antibiotic therapy, and (6) lower intestinal bleeding after other lesions have been excluded.

Additional indications for surgery noted by Welch, Allen, and Donaldson[51] were: diverticulitis in patients under 50 years of age since the disease is more severe in the young, patients demonstrating severe persistent deformity of the sigmoid on radiologic examination, and patients in whom cancer cannot be excluded. Both of these groups and Colcock[11] agree that more and more patients should be considered for one-stage procedures, that the mortality and morbidity could be reduced if the patients were operated upon before some of the disturbing complications of diverticulitis have had a chance to appear, and that multiple stage procedures will continue to have a limited usefulness. Colcock stressed two surgical principles in the therapy of diverticulitis: (1) the acute inflammatory reaction surrounding a perforation of the colon would tend to subside if that segment of the bowel is defunctionalized by a proximal colostomy, and (2) resection and primary anastomosis of a distended obstructed colon is dangerous.

The incidence of bleeding from diverticular disease has been re-evaluated during the past few years. Noer[34] showed that the incidence of bleeding in reported series of diverticulitis varied between 10 and 30 per cent. Injection studies showed an increased concentration of vessels in the bowel wall in the area of the diverticula. Vessels were also found crossing from the serosal toward the mucosal surface of the bowel where many of the diverticula occurred, so that these vessels could easily be the source of bleeding, but there were diverticula in areas where there were no vessels. Noer concluded that moderate hemorrhage is a common finding in patients with diverticulitis, that severe hemorrhage may occur, and that there is a great hazard in emergency operations during active hemorrhage. This argument has supported those who favor resection of localized areas of diverticulitis.

Knight[26] found hemorrhage in diverticulitis in 12.4 per cent of private patients and 31.7 per cent of charity patients. One possible explanation for the discrepancy was the later stages of disease common to the charity institutions, although he admits the difficulty in proving such a thesis. It was also suggested that those patients with bleeding might represent extensive rather than localized forms of the disease. Conservative treatment was recommended since in most cases the bleeding will stop. When disease is limited to one segment of the colon, operative removal may be advised, but when the entire colon is involved, surgery becomes a difficult problem because these patients do not tolerate extensive surgery and surgery may be quite difficult in the presence of extensive diverticulosis and diverticulitis.

POLYPS

Recent thinking about the proper treatment of polyps of the colon has undergone as much change as that for diverticulitis, and ranges from those who advocate total colectomy to those who believe there is no proof of a relationship between polyps and carcinoma.

The discovery of more polyps by additional maneuvers during surgical procedures led Deddish and Hertz,[15] among others, to recommend colotomy

and coloscopy when the colon is already known to contain one or more lesions. In 103 patients with radiologically demonstrated adenomas, they found additional adenomas in 46.6 per cent of the patients by coloscopy. In 32 patients with carcinoma, they found additional lesions in 47 per cent by the same technique. Coloscopy requires a meticulously clean colon, separate instruments that can be discarded after being contaminated, impermeable drapes, and changes of gloves between each colotomy.

An even more radical approach to the discovery of polyps has been proposed by Gants, Raymond, and Pope,[21] who suggested opening the entire colon in the antimesenteric taenia in those cases where endoscopy, coloscopy, transillumination, and palpation failed to reveal whether or not additional lesions were present. They reported 10 clinical cases where incisions of varying lengths had been used. We have had no experience with this technique, but believe that the indications for such an extensive exposure must be limited.

Enquist[19] reported an 8-year experience of a cancer detection center for the study of polyps of the colon and rectum. In a total of over 7,600 patients, 11.5 per cent were found to have one or more polyps at the time of the first examination, and another 7.7 per cent were found to have polyps on subsequent examinations, yielding a total of 19.2 per cent or over 1,450 patients. In these people, 2,363 polyps were found in the distal 25 cm. of the bowel. Two or more lesions were found in 38 per cent of the total group with polyps. Statistical analysis of this study led to certain conclusions about the life history of polyp disease: If a patient has polyps discovered by sigmoidoscopy, there is a 4.5 per cent chance of finding additional lesions by barium enema. If polyps are found by sigmoidoscopy, there is a 0.3 per cent chance of finding a frank carcinoma by x-ray. When polyps are found, there is a 22 per cent chance of developing additional polyps. If the polyps are completely destroyed by sigmoidoscopy, there is a 2.7 per cent chance of their recurring in the same location. If all polyps are removed by polypectomy or segmental resection, the chances of developing other polyps in the colon not visualized by sigmoidoscopy are 6 per cent. Among those patients subjected to surgical procedures, 21 per cent had more polyps found at the time of operation than were reported by x-ray preoperatively.

The frequency of multiple polyps occurring either synchronously or asynchronously led several groups to advocate more radical resections. Lillehei and Wangensteen[28] advocated total or subtotal colectomy for polyps because 38 per cent of the patients with an initial diagnosis of carcinoma of the colon and/or polyps were found to have additional polyps in a portion of the colon that was believed to be uninvolved preoperatively and in an area that would not have been removed by the conventional hemicolectomy. They advocate subtotal colectomy with ileoproctectomy for all lesions of the colon in which no ileum or only a very short segment of it needs to be removed.

Teicher and Abrahams[43] recommended subtotal colectomy when the findings are: three or more polyps in different segments of the colon; two or more

polyps, any one of which contains carcinoma; a cluster of polyps in any single area of the colon; or additional polyps in a patient operated upon for a single polyp.

In opposition to this advocacy of more radical excisions of the colon are the opinions expressed by Grinnell and Lane,[24] who studied 1,856 tumors in 1,335 patients with adenomatous polyps and papillary adenomas of the colon. The incidence of lymph-node metastases was correlated with the location of the carcinoma on the polyp. If the tumor is limited to the head of the polyp then wide local removal of the tumor is recommended because the mortality of the more radical resections is greater than the danger of the tumor metastasizing. Thus they recommend colotomy and polypectomy in the treatment of benign pedunculated adenomatous lesions of the colon. Sessile lesions and those showing gross microscopic evidence of invasive cancer should be resected.

The opinions of Helwig[25] with reference to the malignant potential of polyps are worth quoting directly: "Carcinoma of the large intestine may arise directly from the mucosa, but many carcinomas arise in adenomas. Carcinoma in situ in adenomas of the colon and rectum is not capable of metastasis, but carcinoma with invasion of the core or stalk is capable of metastasis.... It is necessary for the surgeon and pathologist to cooperate fully and to exchange information which is understood by both. In this way the pathologist may lead rather than mislead the surgeon."

Spratt, Ackerman, and Moyer,[40] in a complex statistical study, focused attention on the life history of polyps. Several of their statements also deserve quotation: "To date we have not seen nor have we been able to find a case of metastatic carcinoma that originated in a carcinomatous colonic polyp *in which the stalk did not contain neoplastic cells.* . . . These observations are not compatible with the theory that adenomatous polyps degenerate into infiltrating, metastasizing carcinomas of the colon. . . . The theory of the origin of adenocarcinoma of the colon within adenomatous polyps has little to support it." There would seem to be general agreement about the lack of metastasis from carcinomas limited to the tip of the stalk, but there is still some disagreement about whether or not polyps which begin as benign lesions can degenerate into malignant ones. This problem is of more than academic interest since Moyer believes this study is justification for a less radical surgical approach to colonic polyps. Since about four-fifths of the colonic cancers arise in non-polyp-bearing colons, the "polyp-slaying" approach to colonic cancer will be ineffective unless mortality rates can be significantly lowered.

To further substantiate his ideas about the more conservative management of polyps, Grinnell[23] reviewed his experience to determine if any of the patients followed for 3 or more years would have benefited from a more radical approach. This study was divided into six categories, to include those cases which the various advocates of a more extensive resection would have placed in the subtotal colectomy series. In a separate group were placed the 1,753 resections for cancer to evaluate various ideas about the extension of colon resection for patients with known cancer of the colon. The follow-up results

of patients with multiple polyps of the colon showed that only 1 patient out of every 67 could have benefited from a subtotal or total colectomy. In the patients with cancer, only 8 out 66 patients with multiple cancers could have benefited. Thus the maximum possible salvage rate of the more radical resection would have been 0.73 per cent of the total series. Since this is only about one-sixth of the possible operative mortality alone, regardless of whether or not it would have changed the cure rate, the more radical resections did not seem justified to Grinnell. As with many other radical surgical procedures today, it is not so much a question of whether or not the operation can be done with a satisfactory mortality, but whether the operation is justified in terms of what can be ultimately expected of it. We have not been inclined to the more radical resections, and believe, as do some of those with much more experience, that the increased mortality that must be associated with these much more radical procedures will have to be reckoned with before they can be generally adopted.

EXTENT OF RESECTION

Just as there has been variation in the extent of resection proposed for polyps, so there has been similar discussion for carcinoma. Baker, Margetts, and Schutt,[2] State,[41] Ault,[1] and Rosi[38] have all advocated extending resection of the left colon for lesions either in the rectum or sigmoid. For lesions at or below the rectosigmoid level, a total left colectomy with colostomy at the left transverse colon has been advised. For left colonic lesions above this level, Baker and his co-workers advocate preservation of a rectal stump and sufficient length of the left colon to re-establish continuity. Coloscopy is advocated either through the proximal extent of resection or else through a separate colotomy incision. The proximal extent of the lymphatic resection should be extended by stripping the aorta and vena cava up to the pancreas and ligating the inferior mesenteric artery at its origin. Certain technical difficulties, particularly in fat patients, were noted. Limitation of the ability to bring the proximal end down for a primary anastomosis may be dependent upon the length of the middle colic artery. In some cases, it may be necessary to sacrifice the desired limits of resection of the colon itself, but most of the necessary lymphatic drainage can be obtained. In discussing this extension of the Miles operation, or of any procedure for lesions of the left colon, Cattell[2] has sounded a warning which it is well to heed: "I should like to warn those with perhaps more limited experience with resections of the colon that the complications and possible increased mortality rate following total left colectomy are real. One must carefully balance what the immediate and late results will be before one accepts the routine removal of the entire left colon for all left-sided lesions."

An evaluation of the presence of carcinoma in the lymph nodes would be a valuable addition to the surgical care of these patients, and Blatt and Cincotti[4] have proposed the use of a vital dye for staining the lymphatics during surgery for rectal cancer. Evans blue dye was injected submucosally

through an anoscope within 12 to 72 hours preceding the operative procedure to give the lymphatics time to take up the dye. Stained nodes were free of cancer while nodes which failed to take the dye were found to contain cancer either grossly or microscopically. Cohn, Leon, and Strug[8] had excellent results with another vital dye, direct sky blue, when similarly used to stain nodes arising from the stomach, pancreas, or lungs, and recommended this dye because it can be used during the operative procedure.

In contrast to the recommendations for more extensive resections of the left colon has been the series of articles in favor of a more conservative approach to lesions lying in the controversial area between 5 and 15 cm. from the dentate line. Several authors, notably Waugh[48, 49] and Mayo,[29, 30] have advocated sphincter-saving operations for lesions in this area, and have reported their large experience with these lesions showing satisfactory follow-up results as well as low mortality and morbidity rates. Mayo and associates found an over-all 5-year survival rate of 60 per cent with anterior resection for lesions in this area versus a 5-year survival rate of 52 per cent for combined abdominoperineal resection. The anterior resection group had a more favorable result in both those with and without lymphatic metastasis. Waugh and Turner reported similarly successful results with lesions of the mid-rectum treated by abdominoperineal resection with sphincter preservation.

When an ileostomy or colostomy is required, it is well to take note of the new mucosal eversion technique with mucosa-to-skin suture. The technique was originally proposed by Brooke[5] for an ileostomy, and the physiologic explanation for its satisfactory function and explanation of the "ileostomy maturation" was provided by Turnbull[46] and Crile and Turnbull.[14] At about the same time the technique was applied to colostomy care by Butler,[6] and later by Lemmer and Mehnert,[27] and has gained a wide general acceptance because of its satisfactory performance.

NEWER IDEAS IN CANCER

Of all the more recent developments, those that seem to hold the most promise and are most intriguing revolve around some of the newer concepts in the detection and therapy of cancer.

Several groups have been interested in malignant cells in the venous drainage of the area of malignancy and in the presence of malignant cells in the peripheral circulation. Fisher and Turnbull[20] found tumor cells in the venous drainage of 32 per cent of resected specimens of colon carcinomas, and thus were led to advocate early ligation of the venous supply to prevent vascular spread during resection of colonic carcinomas. Engell[18] found cancer cells in 59 per cent of the samples from the local area of carcinomatous colons. There was no significant difference in the number of cells before and after surgical manipulation. It was not possible to base a prognosis on the finding of tumor cells in the veins draining the tumor area, since tumor cells were found just about as frequently in those patients who subsequently survived as those who died from the tumor. Cancer cells were found too infrequently

in the peripheral blood to be of any value in the operable cases. Roberts and his associates[37] reported contradictory results and noted cancer cells in the peripheral circulation in 16.7 per cent of patients with curable lesions, and 31.1 per cent of those with incurable lesions. He also reported an increase in the number of cells in the peripheral blood during manipulation of the tumor area. Since no cancer cells were found in the peripheral blood of patients with early lesions, this test was not thought to be of value as a screening procedure. Moore and Sako[33] found no cancer cells in the peripheral blood of 40 patients with resectable lesions of the colon or rectum, and found cells in only 1 out of 17 patients with nonresectable lesions. But the blood from the area of the tumor was positive in 16 per cent of the resectable cases and 37 per cent of the nonresectable cases. Microscopic studies of the veins revealed invasion in 65 per cent of the resectable colon lesions, showing a wide discrepancy between the number with detectable circulating cells and those with actual invasion of the veins. Another most important observation of this study was the finding of cancer cells in the peritoneal washings of 35 per cent of both the resectable and nonresectable cases.

The possibility of implanting malignant cells during operation for carcinoma of the breast has been realized for years by almost all surgeons, but strangely enough this same line of reasoning has not been applied to cancers of the gastrointestinal tract until Cole[12] and Goligher, Dukes, and Bussey[22] reported independently, but almost simultaneously, that this might be an explanation for some recurrences in the anastomotic line in colon cancer. Cole noted local implantation in the suture line that could have explained recurrences in 10 per cent of his personal series of 55 cases. At almost the same time, the British group reported a series of 162 cases, in 15 of which intraluminal spread could not be completely eliminated.

Subsequently Beal and Cornell[3] found recurrence at the site of anastomosis in 15 per cent of 140 patients. While they believe this tends to support the ideas proposed by Cole, they also mention the possibility of papillomata playing a role, and the possibility of some of these "recurrences" being due to new lesions.

As a result of his own studies, Cole[12] recommended that tapes be tied around the bowel both proximal and distal to the lesion before any extensive manipulation of the tumor was undertaken so that no further spread within the lumen of the colon would occur. He also advocated irrigating the ends of the bowel thoroughly before the anastomosis was made so that any remaining cancer cells would not be implanted by the suture material. Originally, distilled water was used for this irrigation. Subsequent studies have shown Clorpactin and nitrogen mustard to be the most effective agents,[17, 39] although there is preliminary evidence to show that other agents such as Dakin's solution may be equally effective for irrigation of the bowel ends.

The idea that suture line recurrence may be related to intraluminal spread of cancer cells has been strengthened by careful studies of the presence of cancer cells within the lumen of the bowel.[17, 31, 39] Smears from the mucosal surface of the bowel revealed cancer cells proximal to the lesion in 42 per cent

of the cases and distal to the lesions in 65 per cent of the cases. The closer to the tumor the smears were taken, the higher the incidence of positive smears. Smears taken outside the ligatures were negative for cancer cells. Thus, the placing of ligatures around the bowel would decrease the likelihood of those cells being milked into other parts of the bowel during the operative procedure and thus reduce the chances of cancer implantation in the suture line.

To limit the spread of cancer of the colon at the time of operation, Pomeranz and Garlock[36] designed a colon cover consisting essentially of a gauze pack, to cover the tumor during the operative procedure to prevent peritoneal seeding during operative manipulations.

Another plan to extend the cure rate in some abdominal cancers has been the proposal by Wangensteen[47] to institute a "second look" to determine if any metastases are present and if possible to remove them. In one report of 141 second-look procedures in 103 patients, the plan was outlined as an abdominal re-exploration every 6 months after the primary operation until such time as a negative exploration has been performed after which further explorations no longer seemed indicated. The best results were reported in cancer of the colon, though the procedure had been advocated for a variety of intra-abdominal lesions. In 4 out of 15 cases of cancer of the colon where a second look had revealed cancer, subsequent operations had revealed the patient to be free of cancer, and therefore a second look was thought beneficial in some cases. It was concluded, "The second look is a clinical experiment. We cannot at present recommend its general acceptance but only suggest that an open frame of mind be used in its scrutiny and that the tentative success so far achieved in a few patients be measured against the utter hopelessness of recurrent cancer in the past." Our own attitude has been that a routine second look cannot yet be recommended, but if a patient returns with some new intra-abdominal complaint, such as gallstones or an incisional hernia, this should be used as an opportunity to take a "second look."

The promise of chemical agents that can combat cancer has been the dream of clinicians for many years. A number of such agents are now under investigation and cancer of the colon is one of the areas that appears to offer a fertile field for this kind of clinical study. Economou, Mrazek, and Cole[16] have summarized their experimental data with a specific tumor studied in rats, and the response of this tumor to various forms of chemotherapy, mostly involving the use of nitrogen mustard. They evaluated experimentally the administration of nitrogen mustard intravenously, intraportally at operation, and intraperitoneally. Any method of administration of nitrogen mustard lowered the incidence of tumor takes, but the best results were obtained with intraportal administration at the time of injection of the cancer cells. On this basis they began using nitrogen mustard in patients with various types of cancer, including colonic cancer. Nitrogen mustard (0.1 mg. per kilogram of body weight) was given into the portal vein at the time of resection, a similar amount instilled into the peritoneal cavity at the end of the

operation, and then similar amounts given intravenously on the first 2 postoperative days. Certain dangers were noted. Nitrogen mustard is not safe in patients over 71 years old. It should not be used in a total dose of over 30 mg. for the four doses. It increases the patients' need for transfusions over that needed by similar patients having the same operation but not receiving nitrogen mustards. It depresses the granulocytic elements of the blood. Antibiotics should be used to lessen the risk of infection secondary to the leukopenia. Nausea and vomiting may be troublesome. There is no evidence of delayed wound healing in patients receiving nitrogen mustards. Subsequently this group has reported on the evaluation of a number of agents studied for cancericidal properties, and found nitrogen mustard and Clorpactin XCB to be the most effective. Following this study, they recommended irrigating the wounds and peritoneal cavity with 0.5 per cent solution of Clorpactin. We have used nitrogen mustard on a limited basis. The warnings sounded by Cole are important and are real dangers of this method of therapy. The drops in both red and white cell counts can be severe, and must be watched each day before beginning the next day's therapy. We have not tried either intraperitoneal or intraportal nitrogen mustard, but have given the drug systemically on the day of operation. The reaction to nitrogen mustard is much more intense when the drug is administered on the day of operation than when the same amount of drug is given a patient who has not been subjected to a comparable amount of stress. It is important for anyone using this drug to understand this. We have made the upper age limit 61 instead of 71 as advocated by Cole, since we have found the response in the older group too drastic.

As an extension of the chemotherapeutic attack against cancer, Creech, Krementz, Ryan, and Winblad[13] have recommended use of the extracorporeal circuit as a means of temporarily isolating and maintaining a tumor-bearing area while it was perfused with maximal amounts of some agent, such as nitrogen mustard. They reported using the technique on some gastrointestinal lesions, including those in the colon, but it was too early to appraise the results of this form of therapy.

SUMMARY

If progress in the care of surgical problems of the colon continues at the rate of the past 5 years, the future for those with lesions of the colon should become increasingly bright.

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Erratum

In the July, 1959, issue of the JOURNAL (Vol. 46, pages 22-29), the legends of Figs. 4, 5, and 8 in the article by Drs. John W. Sullenberger, William G. Anlyan, and William T. Weaver, entitled "Serotonin in Intravascular Thrombosis," should read as follows:

Fig. 4.—5-HIAA excretion and platelet counts following 20 mg. of hydrocortisone intravenously. Hydrocortisone (20 mg.) caused a slight elevation of urinary 5-HIAA.

Fig. 5.—Urinary 5-HIAA excretion following operative stress. Daily range of 5-HIAA excretion in patients undergoing a variety of surgical procedures and open cardiotomy with aid of a pump-oxygenator with average daily mean of both groups.

Fig. 8.—Effect of repeated infusion of thrombin on urinary 5-HIAA. Repeated infusions of thrombin at intervals of several days resulted in a progressive diminished response in the excretion of 5-HIAA.